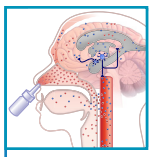
Physiol Rev 98: 1805–1908, 2018
Published June 13, 2018; doi:10.1152/physrev.00031.2017

THE OXYTOCIN RECEPTOR: FROM INTRACELLULAR SIGNALING TO BEHAVIOR

Benjamin Jurek and Inga D. Neumann

Department of Behavioural and Molecular Neurobiology, Institute of Zoology, University of Regensburg, Regensburg, Germany



Jurek B, Neumann ID. The Oxytocin Receptor: From Intracellular Signaling to Behavior. *Physiol Rev* 98: 1805–1908, 2018. Published June 13, 2018; doi:10.1152/physrev.00031.2017.—The many facets of the oxytocin (OXT) system of the brain and periphery elicited nearly 25,000 publications since 1930 (see **FIGURE 1**, as listed in PubMed), which revealed central roles for OXT and its receptor (OXTR) in reproduction, and social and emotional behaviors in animal and human studies focusing on mental and physical health and disease. In this review, we discuss the mechanisms of OXT expression and release, expression and binding of the OXTR in brain and periphery, OXTR-coupled signaling cascades, and their involvement in behavioral outcomes to assemble a comprehensive picture of the central and peripheral OXT system. Traditionally known for its role in milk let-down and uterine contraction during labor, OXT also has implications in physiological, and also behavioral, aspects of reproduction, such as sexual and maternal behaviors and pair bonding, but also anxiety, trust, sociability, food intake, or even drug abuse. The many facets of OXT are, on a molecular basis, brought about by a single receptor. The OXTR, a 7-transmembrane G protein-coupled receptor capable of binding to either $G\alpha_i$ or $G\alpha_q$ proteins, activates a set of signaling cascades, such as the MAPK, PKC, PLC, or CaMK pathways, which converge on transcription factors like CREB or MEF-2. The cellular response to OXT includes regulation of neurite outgrowth, cellular viability, and increased survival. OXTergic projections in the brain represent anxiety and stress-regulating circuits connecting the paraventricular nucleus of the hypothalamus, amygdala, bed nucleus of the stria terminalis, or the medial prefrontal cortex. Which OXT-induced patterns finally alter the behavior of an animal or a human being is still poorly understood, and studying those OXTR-coupled signaling cascades is one initial step toward a better understanding of the molecular background of those behavioral effects.

I. INTRODUCTION AND HISTORY OF OXYTOCIN AND VASOPRESSIN RESEARCH

The scientific interest in the oxytocin (OXT) system has been boosted by the discovery of a plethora of behavioral and physiological effects in animals and humans alike in the last 30 yr. These studies are rooted in more than 100 yr of neuropeptide research, which we will briefly summarize in a historical perspective to gain a better understanding of present developments of OXT research from basic studies into a translational approach.

The closely related nonapeptides OXT and arginine vasopressin (AVP), which are synthesized within neurons of the hypothalamus, substantially form the hypothalamo-neurohypophysial system (HNS) in mammals. Due to its specific anatomy and physiology, this system has become a textbook example that has been studied for more than 100 yr. Harold Gainer has described the HNS as "a veritable 'Rosetta Stone' for neuroendocrinology and neuroscience" (364, 651). Indeed, we know far more about the OXT and AVP systems than about any other neuropeptide or neuroendocrine system, as many seminal findings on neurophysiological or neuroendocrine regulation have been revealed using the HNS.

We can trace back the roots of OXT and AVP research to the work of G. Oliver and E. A. Schäfer, who revealed first physiological effects of the pituitary gland and its extracts in 1895. Specifically, they were the first to show vasopressor effects, which were characterized by W. Howell as effects of

the posterior (infundibular) portion of the pituitary a few years later (456). These observations were based on important anatomical contributions by S. Ramon y Cajal, who described a neuronal pathway from the supraoptic nucleus (SON) of the hypothalamus to the posterior pituitary in 1894. Shortly thereafter, in 1906, the English researcher Sir Henry H. Dale found—rather incidentally and reported as a side note—that a pituitary extract applied to an early pregnant uterus of a cat has uterine-contracting properties (227). The proposed pituitary principle has later been named *oxytocin* from the Greek words ὀξύς, *oxys*, and τόκος, *tokos*, meaning "quick birth." These very first discoveries on physiological effects of posterior pituitary hormones opened the way for its therapeutic use in obstetrics. The clinical use of OXT started with the first case descriptions of infundibular extracts (also called extracts of the infundibular body including the pituitary stalk and the posterior pituitary at this time) "...to produce contractions of the uterus in many serious obstetric complications" in 1909 by the Canadian W. Blair Bell (71).

The third major hormonal function of pituitary extracts was discovered by Ott and Scott in 1909 and by Schäfer and Mackenzie in 1911, who described its ability to trigger milk ejection from the mammary gland (791, 914).

It is of interest to note that it was only in 1928 that O. Kamm used dialysis membranes to separate the vasopressor and the oxytocic principles of pituitary extracts (pituitrin) (505).

The demonstration of cytoplasmic vesicles in specialized glandule-like giant cells in the hypothalamus (later called magnocellular neurons) of teleost fish by the German-born researcher Ernst Scharrer and his wife Berta in the 1930s further paved the way for the definition of neurosecretion (915, 916) **(FIGURE 1)**. However, it is the British physiologist Geoffrey Harris, who is often called the "father of neuroendocrinology" not only because of his pioneering work on the hypothalamo-adenohypophysial system, but also because he furthered our physiological understanding of the posterior pituitary. He could show that electrical stimulation of the neuronal supraoptic-hypophysial tract elevates the intramammary pressure and results in the ejection of milk from a cannulated duct in anesthetized lactating rabbits. Based on this finding and on earlier experiments demonstrating that blood from milked cows could trigger milk ejection in the isolated udder (306), he hypothesized that the posterior pituitary contains a neurosecretory, i.e., releasable factor, which stimulates the observed milk letdown (213, 214). These early ideas of a neurosecretory origin of posterior pituitary hormones (613), of OXT and AVP synthesis in magnocellular neurons of the hypothalamus and their transport via axonal connections within the pituitary stalk to the posterior pituitary (neurohypophysis), are still valid until today.

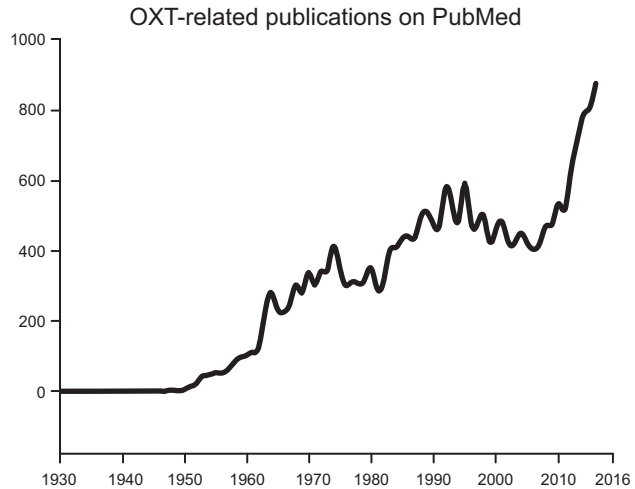


FIGURE 1. Number of OXT-related research articles per year listed in PubMed from 1930 to 2016.

However, true neuropeptide chemistry only started in 1953 with the first successful sequencing of OXT after its isolation from lyophilized posterior lobes of beef pituitary glands by Vincent du Vigneaud (288, 290). Subsequently, he and—independently—Roger Acher succeeded in synthesizing OXT (and later AVP) (5, 289). It is less well known that du Vigneaud's work on OXT was a result of his original interest in insulin, which he described at no less an occasion than the Nobel Lecture on the 12th of December in 1955 that OXT was a result of a "trail of sulfa research."

Shortly after, the development of synthetic agonists and antagonists of OXT and AVP (666, 668) was an essential step into studies on the OXT receptor (OXTR) pharmacology, and the true starting point of a plethora of studies on neuronal, behavioral, and physiological effects of these nonapeptides. Indeed, new vistas into OXT and AVP research were opened with the demonstration of effects of synthetic OXT and AVP and their analogs on various aspects of behavior, which will be discussed in detail later. Here, in this brief historical overview, only the pioneering work of David de Wied and his colleagues (93, 248), who revealed memory effects of synthetic AVP and OXT, and by Cort Pedersen in the 1970s (809) reporting that synthetic OXT induces maternal behavior in rats, will be outlined. Notably, the first demonstration of a nonapeptide effect on behavior in any species appeared in 1955 (1090): administration of vasotocin—the bony fish homolog of AVP—in the form of a pituitary extract induced a "spawning reflex" in the killifish (*Fundulus heteroclitus)* similar to that observed during normal spawning activity.

In the 1980s, the first immunohistochemical demonstration of neurophysin—and later more specifically of OXT- and AVP-containing pathways within the brain (963, 964, 969)—substantiated these behavioral findings. These pathways were described to mainly originate in the hypothala-

mus and to project to extra-hypothalamic target regions, where they may also form synapses (130). These findings lead to the essential question about the general role of the brain OXT and AVP systems, the stimuli activating these pathways and, consequently, triggering brain region-specific local release of OXT and AVP and receptor-mediated effects. In this context, several complementary lines of research furthered the scientific development of OXT and AVP research, which significantly shaped and completed our present picture of the brain neuropeptide systems. Specifically, nonapeptide research has been promoted by the appearance of electrophysiological recordings from hypothalamic neurons, the development of intracerebral perfusion techniques, such as push-pull perfusion and microdialysis, the development of sensitive radioimmunoassays for OXT and AVP for neuropeptide quantification in body fluids and tissues, and by the demonstration of OXT and AVP receptors not only in the periphery but also in the brain.

The first electrophysiological recordings from (magnocellular) OXT and AVP neurons within both the hypothalamic SON and paraventricular nucleus (PVN) started in the 1960s. Brooks and colleagues (1966), who performed their experiments on cats, and Dyball and Koizumi (1969), who used rats, succeeded in associating changes in the activity of SON and PVN neurons with hormone secretion from the hypophysis, for example in response to osmotic stimulation, mechanic stimulation of the nipples by suction, or by stimulation of the uterus of postpartum cats by distension (121, 296). In addition, important milestones were reached by the British and French neuroscientists J. Wakerley, D. Poulain, D. Lincoln, and J. D. Vincent, who recorded from rat or rabbit SON neurons, which were specifically identified as magnocellular neurons projecting to the neurohypophysis by antidromic stimulation of the pituitary stalk (836). In the rat, they could show brief (1–2 s), high-frequency discharges (50 Hz) preceding the abrupt and regular (6–10 min) occurrence of increased intramammary pressure as an indication of milk ejection in the mammary glands (837, 1069). These neuronal activity patterns were later found to be synchronized among OXT neurons of the SON and PVN during the milk ejection reflex in response to the suckling stimulus (69). It was concluded that these synchronized activity patterns provide the neuronal basis for the pulsatile release of OXT necessary to induce appropriate peptide concentrations in plasma and, subsequently, adequate physiological responses of the myoepithelial cells of the mammary glands and of the myometrial cell of the uterus, respectively.

The appearance of intracerebral microperfusion methods such as push-pull perfusion, and later microdialysis, in the context of nonapeptide research in Canada (737), France (714), and East Germany (590, 741) in connection with the development of highly sensitive radioimmunoassays for OXT and AVP (585) allowed monitoring of local neuropeptide release within distinct brain regions. These methods also enabled characterization of the physiological or pharmacological stimuli and the dynamics of such intracerebral release (for review see Ref. 591). With respect to OXT, such central release was, for example, found to be triggered by suckling in the lactating rat (520, 714, 741), during birth (517, 520, 589, 744), and peripheral osmotic stimulation (590) within the hypothalamic SON, but also in extrahypothalamic sites such as the septum, the hippocampus, or the olfactory bulb. At this time, a profound mismatch has often been reported between the demonstration of stimulated local release of OXT on the one hand and the local presence of OXT neuronal fibers or OXTR on the other, mainly due to rather insensitive detection methods. The elegant electron-microscopic work by Morris and Pow (723) revealed that OXT and AVP can be released from all parts of the magnocellular neurons, i.e., also from dendrites and cell bodies, which was of particular interest within the hypothalamic magnocellular nuclei. Later, Ludwig and Leng provided physiological evidence for such dendritic release in the SON (639, 643), which might occur independently of axon terminal release within the neurohypophysis (642, 743).

The detailed description of intracerebral binding sites for OXT (120) and their functional adaptations (472) in the 1980s provided further puzzle pieces for our current understanding of the brain OXT system in a physiological and behavioral context. OXTR are the main target for endogenous and synthetic OXT, and mediate not only the plethora of physiological and behavioral effects but also a great diversity of intracellular effects, which have been largely studied in myometrial cells (904, 976). Therefore, ongoing neurobiological research concerns details regarding their neuron-specific subcellular and brain regional distribution, and endogenous, pharmacological, or environmental factors regulating local OXTR expression. Furthermore, the multiple intraneuronal signaling cascades activated by endogenous or synthetic OXT are an essential prerequisite for OXT actions within the brain, but remain poorly understood. In this review, we will focus on these aspects of the OXTR system, which are essential to consider before intranasally (i.n.) applied OXT can be used as a safe and routine treatment option for psychopathologies associated with socio-emotional dysfunctions such as autism, schizophrenia, or social anxiety.

In fact, the first studies with OXT used as a nasal spray in humans date back to the 1960s, when i.n. OXT was applied to postpartum women to improve the onset of lactation and milk letdown (400, 645). It was only ~40 yr later that i.n. OXT was first applied in the context of brain functions and behavior. In this context, a major breakthrough has been achieved by the description of OXT applied i.n. on neuronal regional activity patterns and on social behavior in healthy men (537, 554), opening the portal to an emerging and still growing number of human studies on OXT. How-

ever, we need to keep in mind that the "historical" discoveries from animal research described above form the essential basis of these studies and provide researchers, who work with humans, with important, although still incomplete, knowledge on the functioning of the brain and peripheral OXT system.

II. EVOLUTION OF THE BRAIN OXT/AVP SYSTEMS

It is interesting to note that the discoveries regarding the OXT and AVP systems described above were mainly achieved in mammals. However, one of the most exciting aspects of nonapeptide research is the fact that the OXT/AVP family is highly conserved in evolution (see **FIGURE 2**; for review, see Refs. 4, 280, 385, 398, 457). So far, more than a dozen nonapeptide homologs have been described in invertebrate and vertebrate taxa. Today, it is well established that a gene duplication of the common ancestor gene, i.e., *vasotocin*, occurred before vertebrate divergence, i.e., between the development of cyclostomes (lampreys) and bony fishes ~450 million years ago. This has mainly been based on the two observations that *1*) only a single nonapeptide is found in invertebrates and primitive vertebrates, and *2*) a high structural similarity between members of the AVP and OXT family occurs with only one or two amino acid substitutions, mainly at *positions 4* and *8* (rarely in *positions 2* and *3*). Specifically, vasotocin and OXT only differ by one amino acid at *position 8*, and vasotocin and AVP only differ at *position 3* (see **FIGURE 2**). Thus most vertebrate species usually possess two nonapeptide forms, including an oxytocin-like and a vasopressin-like form, namely isotocin (Ser^4-OXT) and vasotocin (Ile^3-vasopressin) in teleosts; mesotocin (Ile^8-OXT) and vasotocin in birds, reptiles, and amphibians; and OXT and AVP in mammals (except in pig, where lysine vasopressin instead of AVP is found). Curiously, radioimmunoassays for the detection of plasma OXT levels in squirrel monkeys failed to detect OXT. This inability to detect OXT prompted a sequencing of the OXT coding regions in five species of the family of new world monkeys to identify differences in the OXT peptide. Surprisingly, a single in-frame non-synonymous nucleotide substitution at *position 8* was detected (Leu-8-Pro) in four of the five species (*Saimiri*, *Aotus*, *Cebus*, and *Callithrix*) (598). In addition, secondary duplications of nonapeptide genes are present in a variety of taxa. For example, cartilaginous fishes may express up to six different nonapeptides (385). Secondary duplications are also common in marsupials, which express three different AVP-like forms (AVP, lysipressin, phenypressin) in addition to both mesotocin and OXT (385).

Without going into details of nonapeptide diversity in invertebrates, we just provide a few examples. In "worms," the most primitive species from which a nonapeptide was isolated, annepressin (in annelids) and nematocin (in nem-

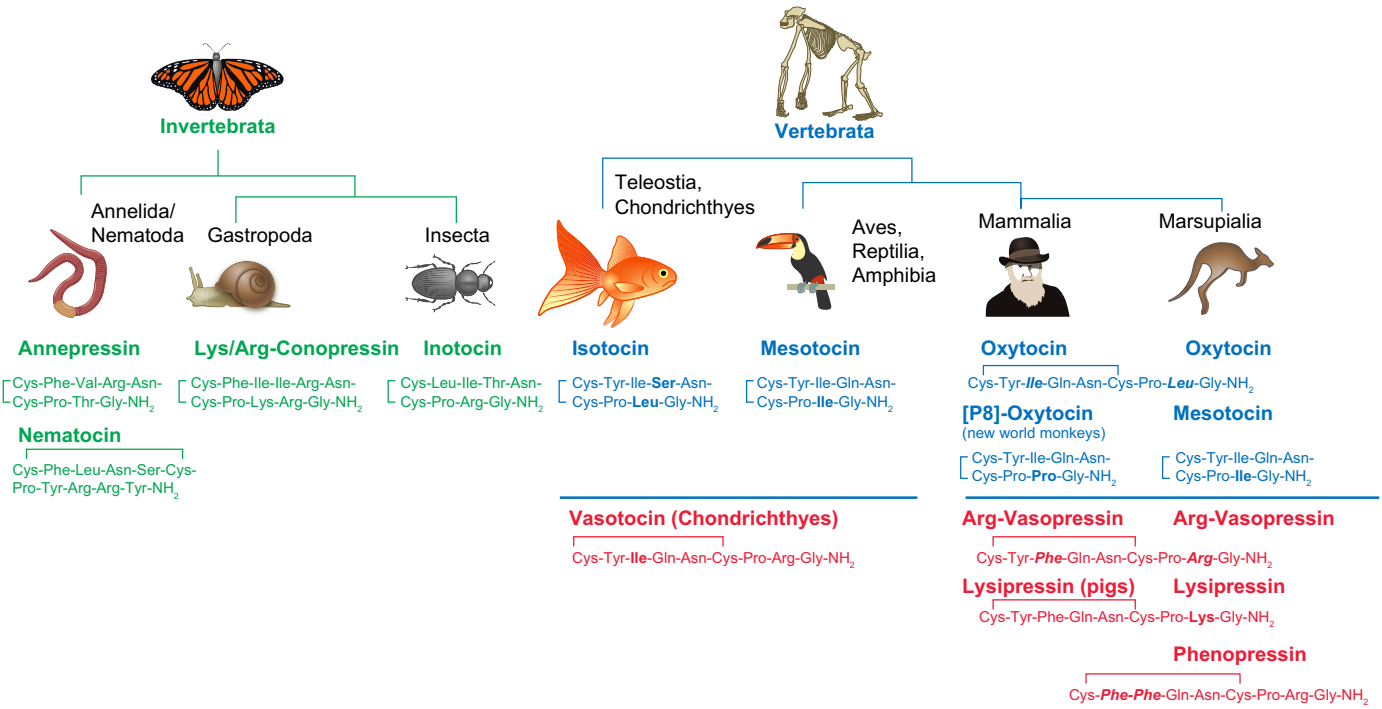


FIGURE 2. Nonapeptide sequences of invertebrate (green) and vertebrate (blue and red) OXT and AVP analogs in the animal kingdom. Each amino acid sequence is initiated by a 19 amino acid signal peptides, followed by the specific nonapeptide sequence depicted above, a processing signal consisting of glycine-lysine-arginine (GKR), and the neurophysin-glycopeptide-COOH-terminus. Italic/bold amino acids, different between OXT and AVP; bold amino acids, different between respective OXT or AVP.

atodes) were found, whereas in snails, cones, sea hare, and leeches, the nonapeptide homolog is called conopressin. In some insects, inopressin is found **(FIGURE 2)**.

The highly conserved biochemical structure of OXT and AVP homologs suggests a strong selective pressure, e.g., by co-evolution with the corresponding receptors. Indeed, their receptors also show a remarkable structural and functional stability throughout evolution (535, 658, 1053).

Each of the mammalian receptor subtypes, i.e., the OXTR, and the AVP receptor subtypes V_{1A}, V_{1B}, and V_2, forms its own distinct group and has originated from a single vasotocin receptor ancestor gene, whose prototype is found in lamprey. Thus the mesotocin, isotocin, and OXT receptors are more closely related to one another than to the AVP receptor subtypes (457). Although there is limited information about receptor evolution to make clear statements about whether and how the receptors multiplied before the peptides did or vice versa, arguments can be found for both opinions (577, 799, 1111). Although we describe the OXTR protein as evolutionary highly conserved (see also Refs. 378, 545) the slight structural change in the [P8]-OXT amino acid sequence that has been found in squirrel monkeys caused compensatory changes in the NH_2-terminal binding region of the OXTR (858). In addition, in the genus *Saguinus* (tamarins), a COOH-terminal serine cluster in the OXTR has been truncated with consequences for β-arrestin binding and subsequent desensitization, receptor recycling, and signaling cascades (see sect. VI and Ref. 1053; reviewed in Ref. 356).

Notably, the structural conservation of nonapeptides and their receptors (with the exception of new world monkeys), is also mirrored by the conservative evolution of the topography of OXT- and AVP-like neurons. Just as OXT and AVP are expressed within the hypothalamus of mammals, their homologs are expressed within similar neurosecretory brain structures of organisms as diverse as worms and fishes.

Moreover, in addition to the conservation of OXT (and AVP) receptor structures, the major distribution of OXTR within the brain of various different mammal species also seems to be conserved as exemplified by OXTR expression within limbic regions relevant for various aspects of social behavior. All these details reflect the evolutionary stability of the nonapeptide system, at least to a certain extent. However, this does not exclude variable and species-specific OXTR expression patterns with widespread differences being observed even in closely related species (for review, see Refs. 385, 398, 1053). These differences in nonapeptide receptor expression clearly contribute to the functional diversity and evolutionary plasticity, which allow species-specific behavioral responses to OXT or AVP as neuromodulators of the brain in a given natural and social environment.

Impressively, also the general physiological and behavioral functions of nonapeptides are remarkably conserved in evolution. For example, the expression and release of isotocin and mesotocin, and of vasotocin—the OXT and AVP homologs, respectively, in teleost fish, amphibians, reptiles, and birds—can be stimulated by hyperosmolality to exert hormonal functions as ion- and osmoregulators. In addition, OXT and AVP homologs play a pivotal role in the regulation of various socio-sexual behaviors in most species. For example, in earthworms and snails, annepressin and conopressin regulate reproductive behaviors, such as reproductive movements and egg laying, respectively (910, 1045). In non-mammalian vertebrates, socio-sexual behaviors regulated by nonapeptides include interspecific cooperative behavior (962), aggression (606), social withdrawal, courtship and sexual behavior, pair bonding in gregarious birds, and egg-lying behavior (for review, see Refs. 514, 541). In sect. VIII, we will describe in detail the profound capacity of OXT to regulate various aspects of socio-sexual and emotional behaviors in mammals by actions on central OXTR.

III. THE ANATOMY OF THE OXT SYSTEM

A. OXT Neurons and Pathways in the Mammalian Brain

OXT is mainly synthesized in magnocellular neurons of the mammalian hypothalamus, specifically within the bilateral SON and PVN (707, 963; see **FIGURE 3**). The clear division of magnocellular neurons between two distinct nuclei (SON, PVN), which possess major axonal projections to the neurohypophysis, does only appear in advanced vertebrates, i.e., in *Amniota* (reptiles, birds, mammals) (397). In addition to the magnocellular neurons of the SON and PVN, a portion of magnocellular OXT neurons of the rat brain are located in the accessory nuclei (866), ventrolateral to the PVN between PVN and SON. OXT neurons of the accessory magnocellular nuclei of the hypothalamus may form an additional origin of OXT projections to various limbic forebrain regions (244, 544; see below).

OXT synthesis also occurs in parvocellular neurons of the PVN and scattered hypothalamic and extra-hypothalamic neurons (244, 544, 545, 963) **(FIGURE 3)**. The parvocellular OXT neurons are clearly distinct from magnocellular neurons, since they are smaller and do not possess projections to the neurohypophysis. However, parvocellular neurons of the PVN were found to project extensively toward the brain stem and spinal cord, where they form synaptic contacts (986) thought to be involved in autonomic functions, pain regulation, and analgesia (305). Moreover, parvocellular

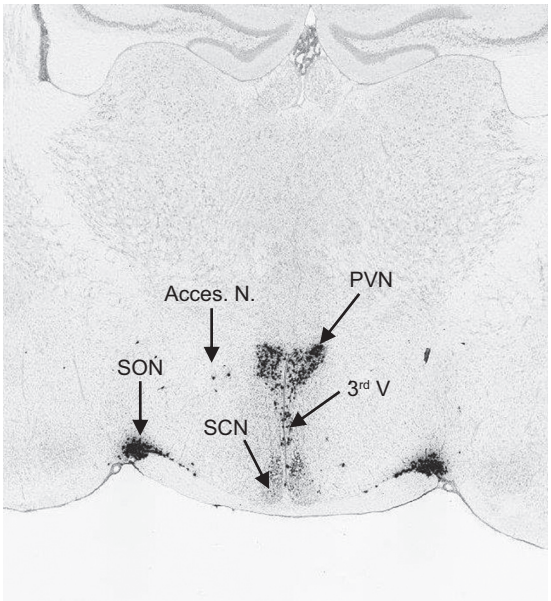


FIGURE 3. Coronal section of an adult mouse brain showing prominent OXT mRNA expression in the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON), and weaker expression along the walls of the third ventricle and the accessory nuclei, as revealed by in situ hybridization. The weak signal detected in the suprachiasmatic nucleus (SCN) is likely to be unspecific and could not be confirmed by immunostaining. Image credit: Allen Institute.

OXT neurons of the PVN seem to connect to the ipsilateral SON and to the contralateral PVN, where they form axo-somatic and axo-dendritic synapses and may control OXT neuronal activity (305, 453).

As an evolutionary mechanism, axons and/or dendrites of OXT neurons are found in close proximity of the third ventricle of the brain and even in between ependymal cells, contacting directly the CSF (591). This implies that either these neurons function as biochemical sensors of the cerebrospinal fluid or the nonapeptides are released directly into the CSF. In addition, magnocellular OXT neurons possess extended dendritic trees, which form the basis for the somato-dendritic release of OXT within the hypothalamic SON and PVN (643, 744, 750, 838). Somato-dendritic release of OXT within the SON and PVN is likely to facilitate autocrine and paracrine regulation of OXT neurons under specific demand, for example, during lactation (718, 740) or during birth (739). Thus, released from somato-dendritic hypothalamic structures, local OXT is likely to contribute to a coordinated neuronal activity of OXT neurons, e.g., during the milk ejection reflex or during labor, resulting in a pulsatile release of OXT into blood (for details on central and peripheral OXT release, see sect. IV*G2*).

Since OXT was found to exert many behavioral effects due to actions at various forebrain and mesolimbic brain sites, the question of extrahypothalamic projections of OXT neurons is still of enormous importance. Originally, using immunohistochemical or lesion techniques, OXT fibers were only found in a few forebrain regions such as the bed nucleus of stria terminalis (BNST) and septal nuclei of various species, including rats (128, 274, 398, 544, 963, 964) and non-human primates (142, 510, 1079). In support, electrical stimulation of the PVN triggered OXT release in the rat septum (741). Based on the recent methodological progress and the advent of fluorogold- (885, 887) and viral vector-based pharmacogenetic and optogenetic (544) techniques, a major breakthrough was achieved by demonstrating that even magnocellular OXT neurons extensively project to various forebrain regions, including the prefrontal cortex, anterior olfactory nucleus, nucleus accumbens, lateral septum, hippocampus, and medial and central amygdala (274, 398, 544, 692a, 963). Such long-range axonal projections to the forebrain can only be found in advanced vertebrates (mammals, reptiles), indicating the co-evolution with complex social and emotional behaviors. However, the number of OXT axons varies substantially between brain regions and is in general rather low (544). This may explain why these fibers were simply overlooked in the past.

The finding that specialized magnocellular OXT neurons of both the SON and PVN (which are mainly considered to project to the neurohypophysis) develop axon collaterals projecting to various forebrain regions is of major importance. First, the existing mismatch between the demonstration of OXT release, OXTR expression, and binding within distinct brain regions on the one hand and the lack of local OXT neuronal connections on the other hand has been largely dissolved. Second, the above-described ascending OXT fibers are the substrate of local OXT release in the respective brain target regions (see below). They provide the neuroanatomical basis for the description of coordinated, but also partly independent, release of OXT into blood and within distinct brain regions (see sect. IV, *E* and *F*). Since various subgroups of OXT neurons may innervate distinct brain regions (545), it can be hypothesized that certain stimuli selectively activate neuronal populations with specific intracerebral projections, in addition to magnocellular OXT neurons projecting to the neurohypophysis. Thus the stimulus- and region-dependent intracerebral release of OXT (591, 746, 750) has found its neuroanatomical basis. To exert neuronal effects, locally released OXT binds to local OXTR, which are expressed within or in very close distance to the target region, for example on synapses, as well as on axons and glial processes (702). Alternatively, although rather unlikely, OXT may diffuse over longer distances to bind to adjacent OXTR (see below and Refs. 591, 643, 702).

B. OXTR Expression in the Adult and Developing Rodent Brain

In the mammalian brain, widespread OXTR expression and OXT binding to its receptor were described, although the OXTR seems to be generally expressed at rather low

levels. Methodological pitfalls limit our knowledge regarding detailed OXTR distribution in the brain **(BOX 1)**. Specifically, the commercially available antibodies for rat and mouse OXTR seem to lack specificity (1116). However, studies quantifying either local *Oxtr* mRNA (220, 703) or using OXTR reporter mice (441, 616, 1116) identified brain regions that express the OXTR in the adult rodent brain, such as the central, medial, and basolateral amygdala, nucleus accumbens, BNST, PVN, medial preoptic area, ventromedial nucleus of the hypothalamus, hippocampus, ventral pallidum, periaqueductal gray, striatum, lateral septum, ventral tegmental area, and olfactory bulb (397). A comprehensive list of brain areas that have been identified to express the OXTR in the rat and mouse brain can be found below **(TABLE 1)**. Moreover, we discuss in more detail the four most prominent and best-understood OXTR-expressing brain regions, i.e., the hypothalamus, prefrontal cortex, hippocampus, and amygdala, also considering species, sex, and cellular differences in OXTR expression.

1. Hypothalamus

The overall OXTR expression level in the PVN of mice, humans, or common marmosets is relatively low (499, 635, 920) and is only detectable by highly sensitive methods, such as single cell RT-PCR (220), or by prior upregulation of the expression using an OXTR antagonist (357). Although expression levels of the *Oxtr* gene in the brain are modulated by sex steroids (65, 1120; and sect. V), OXTR expression in the hypothalamic PVN is similar between males and virgin females (702), and seems to be stable over the estrous cycle and during early to mid-pregnancy (*days 13–15*) (1120). However, an increase of *Oxtr* mRNA in the rat PVN at mid-gestation (*day 15*) and late gestation (*day 20*) has been detected (65).

Interestingly, OXTR-expressing neuronal populations within the hypothalamic PVN are not uniform, but are comprised of neurons with separate electrophysiological and transcriptional characteristics, causing differential responses to OXT (220, 221, 1067). For example, the majority of oxytocinergic and vasopressinergic magnocellular neurons in the PVN do not express the OXTR, but the small population that do express the OXTR divide into 40% corticotropin releasing factor (CRF)-positive and 60% CRF-negative neurons (221). In contrast, OXTR-positive parvocellular neurons are exclusively of the non-CRF type. In addition, OXTR-expressing neurons in the PVN are exclusively glutamatergic, whereas OXTR neurons in the BNST are GABAergic, as indicated by GAD67 (for GABA) or VGLUT2 (for glutamate) expression, respectively (221).

OXTR expression was also found in the ventromedial nucleus of the rat, mouse, and guinea pig hypothalamus (38, 39, 287, 1027, 1031), which is under the control of testosterone and its metabolites estrogen and dihydrotestosterone (39, 52, 493). In contrast to the PVN, ventromedial hypothalamic OXTR expression is higher in male than in female rats (52), and ovariectomy as well as castration reduce *Oxtr* mRNA levels in both sexes (52, 53). However, some species, such as the golden hamster, lack the expression of the OXTR in the ventromedial nucleus of the hypothalamus, indicating species-dependent differences (291).

Astrocytes isolated from embryonic hypothalami also express the OXTR, and this expression is controlled by factors

BOX 1. Methods and problems to detect the OXTR: Analysis of *OXTR* mRNA, OXTR protein, and OXTR binding

The formation of OXTR proteins in tissue or cell culture is, as of every protein, a two-step process of mRNA transcription and translation of the mRNA into protein. To measure local transcription of the *Oxtr* gene, researchers can either apply *1*) in situ hybridization using a fluorophore or radioactive (^{35}S-UTP) labeled oligonucleotide probe specifically designed to bind *Oxtr* mRNA or *2*) quantitative real-time PCR (qPCR). The in situ hybridization approach allows regional localization of *Oxtr* mRNA in brain slices by binding of the labeled oligonucleotide probe to its complementary target strand, thereby detecting expression on a cellular level, along with the downside of low precision of signal quantification. qPCR is a quantitative method to detect *Oxtr* mRNA making use of specific primer pairs that ideally bind within a region that is not subjected to alternative splicing, such as *exon 3* of the *Oxtr* gene, and amplifies the target gene. qPCR is the most sensitive and, if executed correctly, highly specific method. However, qPCR comes at the cost of losing information about spatial expression patterns in tissue.

Both methods detect mRNA of the gene of interest, which is not necessarily predictive of protein levels. Therefore, to confirm the presence of *Oxtr* mRNA, the OXTR protein should be detected and quantified within a distinct brain region using either immunohistochemistry providing a high spatial resolution or Western blotting providing semi-quantitative precision. However, both methods rely on a highly specific OXTR antibody, and commercially available antibodies for rat or mouse OXTR often lack a proof of specificity or, in some cases, have directly been proven to be unspecific (1147). As a useful approach and essential test for specificity, we recommend testing the antibody in OXTR knockout tissue or cells, which becomes more and more easily accessible due to the advent of genome modification techniques, such as CRISPR/cas9.

In addition to the report of mouse (724) or human (548) OXTR antibodies, OXTR-reporter mice have been developed (1147), which enable the detection of the OXTR via the fluorescent protein Venus. However, further generations of reliable antibodies with proven specificity for the OXTR of rats, mice, or voles would significantly simplify and boost OXT-related basic research.

The direct presence of OXTR protein within the brain can also be confirmed by OXTR binding using receptor autoradiography. Thus the binding of a radiolabeled OXTR ligand (e.g. ^{125}I-ornithine vasotocin analog) to its cognate receptor can be visualized in brain slices. This method indirectly infers receptor protein expression by detecting the signal from receptor-ligand complexes. We recommend excluding non-specific binding of the radioligand by testing the ligand in OXTR knockout tissue and competitive binding tests with non-labeled ligand. The advantage of receptor autoradiography is its relatively good spatial resolution, whereas, similar to in situ hybridization, precise signal quantification is limited.

Table 1. *Brain regions that express OXTR*

Brain Region	Intensity	Species
Cortical areas		
Cingulate cortex	++	Mouse, rat,* human
Dorsal peduncular cortex	++	Mouse, rat
Ectorhinal cortex	++	Mouse
Frontal association cortex	+	Mouse
Lateral entorhinal cortex	+++	Mouse
Medial entorhinal cortex	+++	Mouse
Motor cortex	+	Mouse
Orbital/insular/prelimbic cortex	++	Mouse, vole, rat#
Parietal association cortex	++	Mouse, rat*, vole
Perirhinal cortex	+	Mouse, rat#
Piriform cortex, *layers 2* and *3*	+++	Mouse, rat, tuco tuco, human
Retrosplenial granular cortex	++	Mouse, rat*
Retrosplenial agranular cortex	++	Mouse, rat*
Primary auditory cortex	+	Vole
Secondary auditory cortex	++	Mouse
Primary visual cortex	++	Titi monkey
Secondary visual cortex	++	Mouse
Primary somatosensory cortex	++	Mouse
Temporal association cortex	++	Mouse, vole
Anterior olfactory nucleus	+++	Mouse, rat, sheep
Olfactory areas		
Accessory olfactory bulb	+++	Mouse
Granular/glomerular cell layer of the olfactory bulb	+++	Mouse
Olfactory tubercle	+	Mouse, rat#
Tenia tecta	++	Mouse, rat
Basal ganglia and interbrain		
Globus pallidus	+	Mouse
Ventral pallidum	+	Mouse, rat#
Nucleus accumbens	+	Mouse, rat*, tuco tuco, vole
Caudate putamen	+	Rat*, vole
Islands of Calleja	+++	Rat,# sheep
Lateral septal nucleus	+++	Mouse, rat*, titi monkey, cynomolgus monkey, sheep, tuco tuco, rabbit, montane vole
Medial septal nucleus	+++	Mouse, rat
Nucleus of the horizontal limb of the diagonal band	+++	Mouse
Septofimbrial nucleus	+	Mouse
Substantia innominata	+	Mouse
Dorsotuberomammillary nucleus	++	Mouse, rat*
Mammillary peduncle	++	Mouse, rat*
Nucleus facialis	+++	Mouse
Hypoglossal nucleus	+	Mouse, rat,* human
Amygdala		
Basolateral amygdala	++	Mouse, rat,* vole, human
Basomedial amygdala	++	Rat*
Central amygdala	+++	Mouse, rat, tuco tuco, human, montane vole
Medial amygdala, dorsal	++	Mouse, rat,# sheep, rabbit
Bed nucleus of the stria terminalis	+++	Mouse, rat,# sheep, vole, not human
Hippocampus		
CA1 region of the hippocampus	+	Mouse, rat, titi monkey, rabbit, tuco tuco, not human

Continued

Table 1.—*Continued*

Brain Region	Intensity	Species
CA2 region of the hippocampus	++	Mouse, not human
CA3 region of the hippocampus	++	Mouse, Taiwan vole
Dentate gyrus	++	Mouse, titi monkey
Dorsal subiculum	+++	Mouse, rat*
Parasubiculum	+++	Mouse, rat
Ventral subiculum	+++	Mouse, rat#
Presubiculum	++	Rat, titi monkey
Hypothalamic areas		
Anterior hypothalamic area	+	Mouse
Lateral hypothalamic area	++	Mouse
Arcuate hypothalamic nucleus	+++	Mouse
Dorsomedial hypothalamic nucleus	+++	Mouse, rat
Lateral anterior hypothalamic nucleus	+++	Mouse
Paraventricular nucleus	+	Mouse, rat,* sheep, not human
Posterior hypothalamic area	++	Mouse
Ventromedial nucleus of the hypothalamus	+++	Mouse, rat,# sheep, rhesus macaque, montane vole, human
Supraoptic nucleus	+++	Mouse
Suprachiasmatic nucleus	+++	Mouse
Medial preoptic area	++	Mouse, sheep, rat,# cynomolgus monkey, rabbit, human
Magnocellular preoptic nucleus	+++	Mouse, cynomolgus monkey
Lateral preoptic area	+	Mouse, cynomolgus monkey
Medial tuberal nucleus	++	Mouse, rat
Supramammillary nucleus	++	Mouse, rat*
Medial mammillary nucleus	+++	Rat*
Lateral mammillary nucleus	+++	Rat*
Thalamus		
Anterior and paraventricular thalamic nuclei	++	Rat*
Xiphoid thalamic nucleus	++	Mouse
Ventral lateral geniculate nucleus	++	Mouse
Circumventricular organs		
Area postrema	++	Mouse
Organum vasculosum of the lamina terminalis	+++	Mouse
Subfornical organ	++	Mouse
Median eminence	++	Mouse
Midbrain-Hindbrain		
Dorsal raphe nucleus	+	Mouse, not human
Median raphe nucleus	+++	Mouse, not human
Nucleus of the solitary tract	+	Mouse, human
Gigantocellular reticular nucleus	+	Mouse
Prepositus nucleus	+	Mouse
Raphe pallidus nucleus	+++	Mouse
Peripeduncular nucleus	++	Mouse
Posterior pretectal nucleus	++	Mouse
Olivary pretectal nucleus	+	Mouse, rat, not human
Periolivary nucleus	+++	Mouse, not human
Periaqueductal gray	+++	Mouse, titi monkey
Area dorsal to substantia nigra	+++	Mouse
Dorsal tegmental nucleus, central	+	Mouse
Dorsal tegmental nucleus, pericent	+	Mouse
Laterodorsal tegmental nucleus	++	Mouse

Continued

Table 1.—*Continued*

Brain Region	Intensity	Species
Ventral tegmental area	++	Mouse, rat
Reticulotegmental nucleus of pons	+	Mouse
Intermediate reticular nucleus	+	Mouse, rat*
Parvicellular reticular nucleus	+	Mouse, rat*
Lateral reticular nucleus	+++	Mouse, rat*
Pontine reticular nucleus	+++	Mouse
Dorsal medullary reticular nucleus	++	Mouse, rat*
Kolliker-Fuse nucleus	+	Mouse
Lateral parabrachial nucleus	++	Mouse
Subceruleus nucleus	++	Mouse
Nucleus O	+++	Mouse
Barrington's nucleus	+	Mouse
Dorsomedial spinal 5 nucleus	++	Mouse
Spinal 5 nucleus, caudal part	+++	Mouse
Spinal 5 nucleus, interpolar part	++	Mouse
Spinal vestibular nucleus	++	Mouse
Medial vestibular nucleus	++	Mouse, rat
Vestibulocerebellar nucleus	+	Mouse
Dorsal nucleus of the vagus nerve	+	Mouse, rat
Cerebellum	++	Mouse
Molecular layer of the cerebellar cortex	++	Mouse

Brain regions that express OXTR, combined data from mice, rats (adult and juvenile), cynomolgus monkeys, coppery titi monkeys, rhesus macaques, rabbits, tuco tucos, prairie, montane, and Taiwan voles, and humans (68, 96, 126, 303, 315, 369, 370, 407, 416, 498, 514, 738, 1003, 1078, 1092, 1169). Binding intensity is depicted as relative values and may differ slightly between species: +, weak expression; ++, medium expression; +++, strong expression; not human, no immunostaining was detected using 2F8 antibody; vole, (unless further specified) prairie, montane, or Taiwan vole. *Transient prenatal and/or early postnatal expression with subsequent decrease in adult life. #Late postnatal onset or increase of expression. Regions not mentioned here have not been assessed for OXTR expression, and, therefore, OXTR expression cannot be excluded.

released from hypothalamic neurons (703). When cultured without neuronal contact, astrocytes expressed the OXTR at low level; but when treated with medium from cultured neurons, astrocytic OXTR level increased, most probably due to neuronal release of TGF-β and uptake by astrocytes (703).

2. Prefrontal cortex

The expression of OXTR in the prefrontal cortex has so far been described in mice, rats, and voles. Using a novel OXTR antibody for mice, a lateralization of OXTR expression in the female cortex with OXTR being more expressed in the left auditory cortex than in the right auditory cortex has been described (670). This lateralization was supposed to play a role in maternal behavior, since pup-retrieval behavior required the left, but not right, auditory cortex. In the medial prefrontal cortex, OXTR expression has been found in interneurons (736), which are characterized by co-expression of CRF-binding protein and GABA (616), somatostatin, and a regular spiking pattern (736). In contrast to regulating socio-sexual behavior in female mice, male mouse OXTR-expressing cortical interneurons are thought to be involved in the regulation of anxiety-like behavior (616).

Also in the rat, OXTR have been detected in the prefrontal cortex, and pharmacological studies indicate their involvement in maternal behavior and anxiety-related behavior. For instance, administration of OXT into the prelimbic part of the medial prefrontal cortex reduced anxiety-like behavior in male and female rats (896), whereas local OXTR blockade by an OXTR antagonist in the medial prefrontal cortex impaired maternal care and increased maternal aggression (895).

In monogamous prairie voles, OXTR expression in the medial prefrontal cortex is higher than in promiscuous montane voles, and female voles of both species display higher prefrontal cortex OXTR expression levels than males (953). In general, OXTR binding in the temporal and parietal association areas of the prairie vole cortex are relatively high in comparison to the auditory or somatosensory cortex (293). In addition, a detectable difference in OXTR expression has been described between cortical layers, specifically, *layer 4* seems to express the

OXTR at very low levels, in contrast to *layers 2*, *3*, and *5* in prairie voles (293). These results indicate a role of OXT in the integration of sensory and motor functions in the vole central nervous system, with implications for the modulation of social interactions in this monogamous species.

3. Hippocampus

OXTR expression and binding have been detected in all subregions of the hippocampus, i.e., the CA1, CA2, CA3, subiculum, and dentate gyrus in OXTR-reporter mice (389, 1116), by receptorautoradiography (291, 473, 488, 646, 789, 1030), immunostaining (702), or qPCR (659) in mice, rats, golden hamsters, syrian hamsters, tuco tucos, naked mole rats, and Taiwan voles (172, 291, 646, 789, 1116).

In the rat hippocampus, highest OXTR density has been found in the CA1 (compared with lesser expression in CA2 or CA3), where its functionality has also been confirmed. In detail, OXTR-expressing hippocampal GABAergic interneurons are excited by the specific OXTR agonist TGOT in vitro (1128). In hippocampal slices, 3 min of bath application with 200 nM TGOT depolarized small hilar OXTR interneurons, which facilitated GABA release not only onto pyramidal cells but also onto mossy cells of the granular layer of the dentate gyrus. This TGOT-induced GABA release produced a robust increase in inhibitory postsynaptic current frequency and amplitude that returned to baseline levels within 10 min (420). The inhibitory effect of OXT turned out to be reversible and transient; however, long-term incubation of hippocampal slices (3 h) with OXT induced CREB-dependent long-term potentiation via the MAPK pathway likely to be involved in spatial memory during lactation (1011).

In vivo, intra-hippocampal OXT infusions have been shown to increase neurogenesis in the ventral, but not dorsal, dentate gyrus and to protect against stress or corticosterone-induced reduction of hippocampal plasticity (612). Although corticosterone administration increased OXTR binding in the hippocampus of male rats, adrenalectomy exerted the opposite effect (617).

4. Amygdala

OXTR expression and binding has mainly been found in the two major subdivisions of the amygdala, namely the central and medial amygdala of rats and mice (997, 1120, but also see Ref. 389). The functional role of amygdala OXTR comprises the regulation of social behavior (152, 327, 407, 649) and fear expression (1067). Expression of the OXTR in the central amygdala is independent of gonadal steroids, and, therefore, central as well as medial amygdala OXTR expression is stable during the estrous cycle in female rats and rabbits, and over the course of pregnancy and lactation (488, 1036). However, OXTR expression in the female central amygdala seems to correlate negatively with social interest, whereas OXTR expression in the male rat medial amygdala correlates positively with social interest (294).

The expression of fear is negatively regulated by OXTR in the lateral part of the central amygdala (462, 974, 1067). In detail, inhibitory effects of OXT on the expression of fear are caused by increased excitability of OXTR neurons in the lateral part of the central amygdala, which project to output neurons in the medial part of the central amygdala and inhibit the motor fear response via GABA release (462). This regulatory function also depends on the dopamine receptor D2, which forms heterocomplexes with the OXTR. A heterocomplex of the OXTR and the D2 receptor facilitates the coupling of the receptors to signaling cascades, namely MAPK and Ca^{2+}-dependent calcineurin signaling, thereby enhancing the anxiolytic effect of OXT (241, and see sect. VI).

5. Subcellular distribution of the OXTR

Using electron microscopy, OXTR protein expression has been identified at various subcellular compartments of cortical neurons, including presynaptic and postsynaptic membranes of putative excitatory synapses, inhibitory synapses located on dendritic shafts, perisomatic and preterminal axon segments, and also microglial membranes (702, 1125). OXTR-immunostaining was lacking within cortical dendrites. The functional role of OXTR at dendritic shafts remains to be determined, but a dominant role for OXT in the regulation of inhibitory GABAergic transmission has been suggested in various studies (131, 670, 702, 793, 956).

6. OXTR expression in the brain during development

In the brain, the OXTR is expressed in a development-dependent pattern (reviewed in Ref. 398; see **TABLE 1**). In general, expression of OXTR in the embryonic or juvenile brain is higher in regions related to reward and social and spatial memory, whereas in adult brains OXTR binding is higher in cortical regions and in regions related to social-decision making (957). Most expression changes occur in two developmental stages in the rat, i.e., around *postnatal week 3* (*postnatal days 16–22*) and during puberty (after *postnatal day 35*) (1029, 1030). In early life (until *postnatal day 10*), some areas showed intense OXTR binding, including the cingulate or retrosplenial cortex (1030), the caudate putamen and lateral septum (646), whereas OXTR binding completely disappeared in the adult cingulate and retrosplenial cortex (1030). In the lateral septum, OXTR binding density of 5-wk-old rats was high and decreased slightly in the adult brain (646).

In contrast, some regions without visible binding in early life show OXTR binding around *postnatal day 40–45*, i.e., in puberty (1030). For instance, OXTR binding increased

fourfold with age in the ventromedial hypothalamus (646, 1030). In the BNST and central amygdala, OXTR binding can also be detected in early life but was found to further increase in puberty (1030).

Those developmental shifts in regional OXTR expression are probably the molecular mechanism underlying social behavioral adaptations to age-dependent social demands (957), such as social play behavior in juveniles (113) or partner preference formation and alloparental care in adult rats and voles (513, 782, 886).

C. OXTR Expression and Binding in the Non-Human Primate and Human Brain

Generally, primates are excellent models to investigate the role of OXT in complex social behavior. However, only recently, Freeman and colleagues succeeded in developing an autoradiographic protocol for selective OXTR binding in primates (354). Thus they could identify OXTR binding sites in the nucleus basalis of Meynert (visual attention), pedunculopontine tegmental nucleus (visual attention and arousal), the superficial gray layer of the superior colliculus (gaze control), the trapezoid body (auditory processing), and the ventromedial hypothalamus (sexual behavior and feeding) in the brain of rhesus macaques (*Macaca mulatta*). In confirmation of this data, local *Oxtr* mRNA expression was identical to the identified binding regions (354).

In another primate, the social monogamous coppery titi monkey (*Callicebus cupreus*), OXTR binding and mRNA were detected in the nucleus basalis of Meynert, but also in regions that were not detected in the macaque, e.g., the CA1 field and dentate gyrus of the hippocampus, layers I and III of the presubiculum, periaqueductal gray, pulvinar, layer 4C of the primary visual cortex in the occipital lobe, deeper layers of the superior colliculus, nucleus prepositus, pontine gray, and spinal trigeminal nucleus. In one animal, OXTR expression was also detected in the lateral septum (355). In brain tissue from an adult cynomolgus monkey, a specific monoclonal human OXTR antibody (termed 2F8; Ref. 532) provided evidence for expression patterns of the OXTR in primates similar to that described in rodents before, since OXTR staining was also found in cell bodies and fibers of the preoptic area as well as fibers in the septal nucleus (91).

In 2013, Boccia and colleagues used the same, obviously specific (see **BOX 1**), monoclonal antibody to stain OXTR in a human female brain (92). In this paper, OXTR expression was predominantly detected in limbic and hypothalamic structures, such as central and basolateral amygdala (fear response, autism) (41, 462), anterior cingulate [decision-making (153), and associated with posttraumatic stress disorder (454) and schizophrenia (1110)] and piriform cortex (learning odors and taste) (167, 224), medial preoptic area (sexual and parental behavior) (550), ventrolateral ventromedial nucleus of the hypothalamus (sexual behavior) (146), nucleus of the solitary tract (gustatory perception, sexual behavior) (549, 930), and hypoglossal nucleus (breathing, speech, vertical eye movement) (780, 928). Surprisingly, no staining was found in the hippocampal CA1 and CA2, BNST, PVN of the hypothalamus, pons, olivary nuclei, and raphe nuclei (92). Although the technique they used seems adequate to detect the OXTR in most regions, brain regions might exist, where OXTR expression falls below the detection limit.

D. Peripheral OXT Synthesis and OXTR Expression

In addition to OXT and OXTR expression and binding within the brain (see **TABLE 1**), there is also expression of the nonapeptide and, in particular, OXTR in peripheral tissues, which has been detected using immunohistochemistry, receptor autoradiography, RT-qPCR, or a combination of these in various mammals, including rats, mice, cow, dogs, baboons, and humans in peripheral organs (see **TABLE 2**).

In comparison to OXTR expression, peripheral OXT synthesis has been detected so far only in few organs, including corpus luteum, uterus, amnion, placenta, interstitial cells of the testes, adrenal glands, heart, dermis, and thymus **(TABLE 2)**. Among the peripheral organs with OXTR expression and binding are the macula densa cells of the renal cortex (790), cardiomyocytes of the heart (189, 408, 822), nociceptive dorsal root ganglion neurons (722), retina (411), adipocytes (299, 1113), and adrenal medulla cells (995).

Additional sites of expression were recently identified with surprising implications for OXT-related functions in the body-brain axis. In detail, OXTR were found in mouse taste buds, where OXT could, in addition to central regulation of satiety, play a direct role in regulating food intake (942; see sect. X*A*). OXTR expression was also described in osteoclasts (198) and osteoblasts (197, 264). In osteoblasts, the membrane-bound form of the OXTR can be internalized and transported to the nuclear membrane and participate in bone maturation, probably via signaling cascades different from those activated by the membrane-bound form of the OXTR. The authors, therefore, hypothesized a direct effect of the nuclear form of the OXTR on gene transcription (264). Future studies need to reveal the contribution of nuclear OXTR signaling in the regulation also of other physiological and behavioral functions.

OXTR expression was further revealed in the intestinal system, specifically in enteric neurons and enterocytes. Chronic activation of those enteric OXTR by osmotic minipumps (delivering OXT systemically via the femoral vein) was recently found to reduce intestinal inflammation, possibly by preventing inflammation-evoked signals to relevant

Table 2. *Peripheral tissues that express OXT and the OXTR and related publications demonstrating cell type- or organ-specific mRNA or protein levels*

Peripheral OXT			Peripheral OXTR		
Both ventricles and atria of the heart, vena cava, and aorta	Rat, human	499, 500	Cardiomyocytes	Rat, human	191, 420, 848
Interstitial cells of testes	Rat, human	353, 416, 787	Testes, rat penis	Rat	62, 1168
Corpus luteum, uterus, amnion	Rat	622, 623	Uterus (myometrium, endometrium)	Rat	994, 995
Placenta	Human, bovine	337	Neonatal anogenital region	Mouse	402
Medulla and cortex of adrenal glands	Rat, human	21, 787	Medulla of adrenal gland, neonatal adrenals	Mouse, bovine	402, 1026
Dermal fibroblasts and keratinocytes	Human	251	Dermal fibroblasts and keratinocytes	Human	251
Thymus	Human	377, 386, 736			
			Taste buds	Mouse	969
			Osteoclasts, osteoblasts	Mouse, human	199, 200, 266
			Enteric neurons and enterocytes	Rats	1116, 1117
			Neonatal oronasal cavity	Mouse	402
			Retina	Mouse	402, 422
			Neonatal eye		
			Neonatal whisker pads	Mouse	402
			Nociceptive dorsal root ganglion neurons	Rat	748
			Macula densa cells of renal cortex	Rat	816
			Adipocytes	Rat, mouse	301, 1145

brain regions, such as PVN, amygdala, and piriform cortex (1084, 1085). Also, the expression of OXT and its receptor has been shown in fibroblasts and keratinocytes of the human skin, which regulate processes involved in atopic dermatitis, such as proliferation, inflammation, and oxidative stress response in the skin (250). Atopic dermatitis is a multifactorial skin disease that aggravates not only upon physiological but also psychological stress (177). The view that peripheral inflammatory processes are regulated by OXT is further supported by studies linking inflammatory skin diseases with psychopathologies associated with a dysregulated OXT system, such as autism spectrum disorder or attention deficit hyperactivity disorder (136, 656, 1109).

The obvious imbalance between the expression of the ligand in limited organs and the widespread expression of its receptor can be explained by the general peripheral distribution of OXT via the bloodstream, which only creates the need for peripheral OXTR expression, and relatively sparse peripheral OXT expression sites.

Neonatal expression of the OXTR was analyzed by receptor autoradiography with sagittal body sections of male and female P0 C57BL/6J mice. Specificity of the radioligand was tested by means of OXTR knockout mice and a competitive binding assay against increasing OXT concentrations (393). OXTR were detected in the neonatal eye, whisker pads, nasal cavity, adrenal glands, and anogenital region. Expression of the OXTR in the neonatal nasal cavity is interesting in light of behavioral effects of intranasal OXT treatment; however, corresponding data in humans are lacking. Interestingly, non-specific binding of the ligand was found in the liver and brown adipose tissue of OXTR knockout mice, indicating a somehow altered composition of fat tissue that resembles binding sites for OXT (393).

IV. REGULATION OF OXT SYNTHESIS, TRANSPORT, AND RELEASE

A. The *Oxt* Gene and Regulation of OXT Transcription

The *Oxt* gene is mainly expressed in hypothalamic neurons of the brain, but synthesis was also found in various peripheral tissues (see **FIGURES 3 AND 4**; sect. II). The relatively small gene (4,580 base pairs) encoding the precursor protein for OXT and its associated neurophysin contains three exons and two introns. The first exon contains the 5′ noncoding promoter region, a small signal peptide, the nonapeptide OXT, and the NH_2-terminal, the variable region of neurophysin. The second exon encodes the central, highly conserved region of neurophysin, and the third exon encodes the remaining

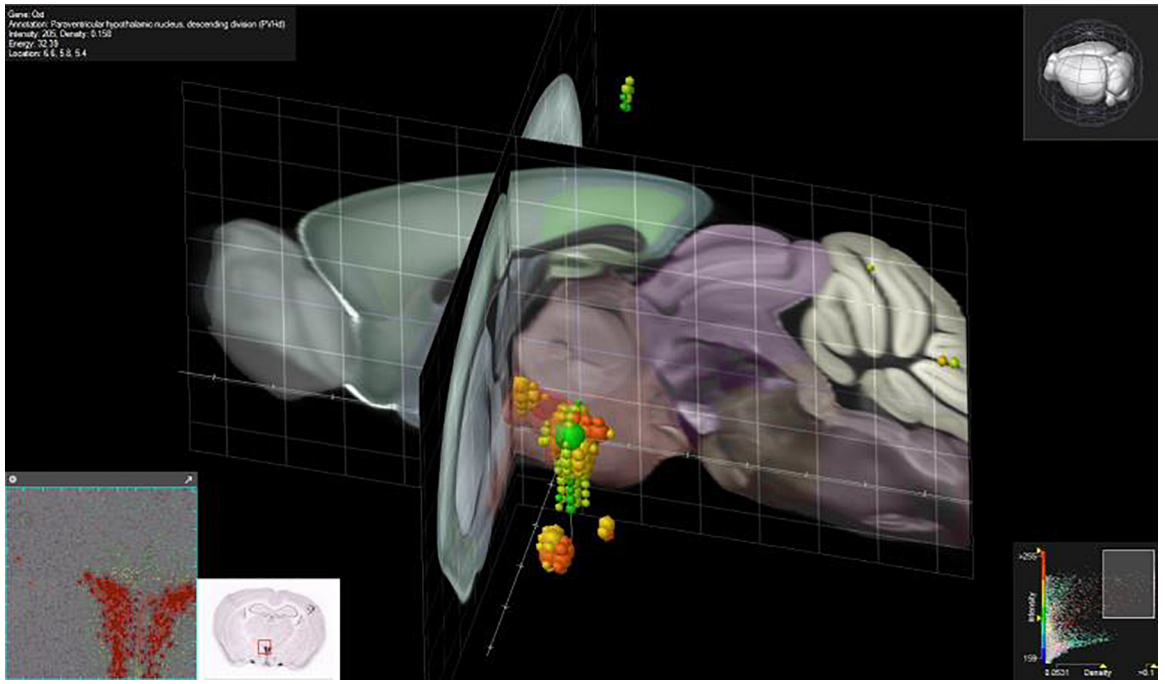


FIGURE 4. Representative OXT expression on a 3D-sagittal/coronal section of an adult mouse brain, using the Allen mouse atlas program. Yellow and red dots represent high density of OXT expression; green dots represent lower expression. OXT expression is mainly found in the PVN, along the third ventricle, and the SON. For detailed information on staining protocol and data source, see http://mouse.brainmap.org/search/show?page_num=0&page_size=32&no_paging=false&exact_match=true&search_term=Oxt&search_type= gene. Image credit: Allen Institute.

COOH-terminus of neurophysin (481). The human OXT precursor is organized as described, comprised of three exons and two introns, but without COOH-terminal glycopeptide moiety as found in the AVP precursors of all mammals (709). In humans, both the *OXT* and the *AVP* gene are located on *chromosome 20* (870) separated by 8 kb (in the rat by 11 kb) (707, 709) **(FIGURE 5)**.

The almost exclusive expression of either *Oxt* or *Avp* in specialized hypothalamic OXT or AVP neurons defines their phenotypes and implies effective regulatory mechanisms for gene activation and gene suppression, respectively. Adeno-associated viral vectors have been used in combination with enhanced green fluorescent protein (eGFP) as a reporter to delete selected promoter sequences of either the *Oxt* or *Avp* gene (334, 335). These studies revealed that the key elements in the gene promoters that regulate their cell-type-specific expression in magnocellular neurons of the SON are located in the 5′-flanking regions of both promoters. In the case of the *Oxt* gene, the regulatory DNA sequence appeared to reside in the −216 to −100 bp upstream of the transcription start site (335), where a cell-type-specific activator of transcription may operate. Evidence for specific suppressors of AVP expression in OXT cells (or vice versa) could not be identified so far (334). In this 5′-flanking region in the *Oxt* promoter, functional estrogen/retinoic acid receptor-like transcription factor binding sites have been localized, which were described as the composite hormone response element (8). This element has the capacity to bind various classical and orphan nuclear hormone receptors (132), such as estrogen receptor β (ER β) (868, 947). Some of these nuclear hormone receptors are also present in magnocellular neurons (463), where they may activate or inhibit OXT promoter gene expression (187, 868). Sharma and co-workers found that the ER β is activated by the dihydrotestosterone metabolite 5α-androstane-3β,17β-diol, leading not only to ER β occupancy of the estrogen responsive element of the OXT promoter but

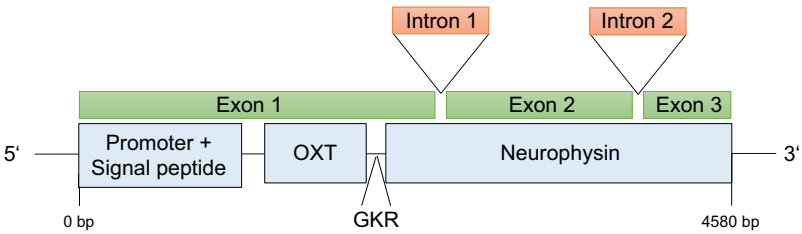


FIGURE 5. Representative scheme of the Oxt gene on human *chromosome 20*, containing three exons and two introns. The gene codes for an initial signal peptide, the nonapeptide OXT, a glycine, lysine, arginine (GKR) processing signal, the variable NH_2-terminal region of neurophysin, the core neurophysin, and its COOH-terminal region.

also to increased binding of the transcription factor CREB and to acetylation of histone H4. These three components form a functional complex that drives OXT expression by activated transcription factors and loose chromatin structure (929) **(FIGURE 5)**.

B. OXT mRNA Translation and Axonal Transport

Translation of OXT mRNA occurs on ribosomes of the rough endoplasmic reticulum as part of the large precursor protein (prepropeptide) consisting of the signal peptide, the nonapeptide, and the neurophysin in the neuronal soma. The signal peptide supports the protein transfer into the Golgi apparatus, where concentration and packaging into newly formed neurosecretory vesicles and extensive posttranslational processing occur (17, 363). Such intravesicular posttranslational processing of the precursor protein includes sequential proteolytic cleavage by special converting enzymes and conversion into the smaller OXT and neurophysin parts, and various protein modifications, among them glycosylation, phosphorylation, acetylation, and amidation (40, 1012). Whereas the physiological functions of OXT as a neurohormone have been extensively studied (see below), the function of neurophysin is still unclear but may include support of axonal transport of neurosecretory vesicles to the neurohypophysis (869).

While undergoing the complex posttranslational maturation process in neurosecretory vesicles, these so-called large dense-core vesicles are targeted to their sites of release via axonal transport, best studied in SON neurons projecting via the eminentia mediana (infundibulum) to the neurohypophysis (124). ^{35}S-labeled protein originating in the SON was found to arrive in the rat neurohypophysis after 2 h (124). Given that the transport of hypothalamic OXT to neurohypophysial terminals also needs ~2 h and that the distance between the hypothalamic magnocellular SON and PVN and the rat posterior pituitary is ~2–3 mm (805), neuropeptide secretory vesicles should travel at a speed of 1–1.5 mm/h. Once arrived in neurohypophysial terminals, OXT-containing vesicles are stored in and released from neuronal terminals into neurohypophysial capillaries and, thus, into the peripheral blood stream via so-called neurohemal contact zones (428) (see below). After enzymatic cleavage from the nonapeptide, neurophysin is also secreted into the blood stream; its functions, however, are unknown.

The hypothalamic synthesis within the SON and PVN and neurohypophysial secretion of OXT into blood are triggered by various specific physiological stimuli as described below (see sect. IV*D*). Briefly, main stimuli for the OXT system in all mammals studied so far include vaginocervical distension as found during birth (Ferguson reflex), suckling during lactation (milk ejection reflex), sexual stimulation, and hyperosmotic and other forms of stress (1, 237, 282, 297, 477, 480, 509, 591, 593, 604, 746, 968, 1049, 1050, 1100, 1102).

C. Intra-neuronal Sites of OXT Synthesis

There is evidence for the presence of OXT (and AVP) mRNA in axons (708) and dendrites (711) as well. However, only dendrites were shown to be capable of local protein synthesis (366, 507, 672, 711, 1115). Dendritic peptide synthesis has specifically been proposed for input-specific delivery of proteins with key functions in synaptic plasticity (971). Also, magnocellular hypothalamic neurons seem to be capable of synthesizing proteins within their dendrites (650), whereas the axonal compartment appears to lack this capacity (710, 1007). It is thus conceivable that OXT (and AVP) synthesis in the somata of magnocellular OXT neurons is the prerequisite for nonapeptide release from axonal terminals into blood (or within central target regions of axonal projections; see below) and for somatic release within the SON and PVN, whereas dendritically released OXT as found in the SON and PVN is synthesized in dendrites. In addition to dendritic nonapeptide synthesis, also large dense-core vesicles and their fusion with the dendritic membrane were visualized in dendrites of magnocellular neurons within the SON using electron microscopy, further supporting the option of dendritic release (838; see below).

D. Mechanisms of OXT Release: Axon Terminal vs. Somato-Dendritic Release

1. Neuronal transport of OXT

After synthesis and package in large dense-cored vesicles, OXT is transported to and stored in neurohypophysial terminals, but also within dendrites of hypothalamic magnocellular neurons. Subsequently, OXT is released from neurohypophysial axon terminals, from axons and/or axon terminals of centrally projecting neurons, and from somata and dendrites within the hypothalamic SON and PVN. This suggests compartment-specific mechanisms of peptide sorting, transport, storage, and release. OXT (and neurophysin)-containing large dense-core vesicles are directed either to the axonal ending or to the dendrites by a protein kinase A- or protein kinase C-dependent mechanism. Activation of protein kinase A enhances the association with two motor proteins (kinesin-2 and ANXA1), thus increasing the axonal localization of OXT vesicles, whereas protein kinase C activation interferes with the binding of kinesin-2 to ANXA1, thereby attenuating the transport to the axonal endings and increasing dendritic accumulation (661).

2. Axon terminal release of OXT

After axonal transport to neurohypophysial terminals and local storage, the release of OXT follows general mecha-

nisms of neuronal exocytosis. Action potentials generated in hypothalamic cell bodies open local voltage-dependent Ca^{2+} channels of the terminal membrane, resulting in Ca^{2} entry and a rise in intracellular Ca^{2+}, which triggers exocytosis of neurosecretory vesicles to release OXT into neurohypophysial capillaries. Magnocellular terminals build close anatomical contacts with these capillaries, so-called neuro-hemal contacts, which lack a blood-brain barrier and thus are characterized by fenestrated contacts between capillary endothelial cells (427). As for all other neuroendocrine systems, such as AVP or CRF and other hypothalamic-releasing hormones into the portal blood circulation of the eminentia mediana, this allows diffusion of OXT into the circulation.

For terminal exocytosis of neuropeptidergic (as well as other) vesicles, the interaction of multiple vesicle- and membrane-associated proteins is essential in forming a complex known as the soluble *N*-ethylmaleimide-sensitive factor attachment receptor (SNARE) complex. The SNARE complex largely consists of the vesicle-associated membrane protein 2 (VAMP-2), syntaxin-1, and soluble *N*-ethylmaleimide attachment protein-25 (SNAP-25), and a number of regulatory proteins such as synaptotagmins, munc-18, and Ca^{2+}-dependent activator protein for secretion (CAPS-1), which are described in detail elsewhere (483, 484, 792, 972). This entire exocytosis machinery has also been identified in neuropeptidergic terminals of the posterior pituitary (640, 844, 1070, 1137).

Importantly, some of these proteins (e.g., syntaxin-1, munc-18, and CAPs-1, vesicle-associated membrane protein 4; VAMP-4, and SNAP-25) were also identified in somata and dendrites of hypothalamic magnocellular neurons, whereas others such as SNAP-25 were not or were localized in presynaptic contact zones of OXT neurons (e.g., synaptotagmin-1 and VAMP-2) (640, 792). Thus, although SNARE proteins seem to be generally required for dendritic neuropeptide release, the detailed contribution of various proteins to the molecular machinery essential for somato-dendritic OXT release within the hypothalamus and from neurohypophysial terminals may substantially differ.

3. Dendritic release of OXT

Like axon terminal secretion, dendritic OXT release has also been shown to be Ca^{2+}-dependent (240, 744). The essential increase in free intracellular Ca^{2+} may have different extracellular and intracellular sources. The entry of extracellular Ca^{2+} mainly occurs via voltage-dependent Ca^{2+} channels (338). Specifically, the N-type voltage-dependent Ca^{2+} channels (348, 498) appear to be important for dendritic OXT release; blockade of N-type channels reduced OXT release within the SON (for review, see Ref. 1008). Ca^{2+} entry via N- as well as L-type channels has also been shown to be essential for somato-dendritic release of other neuromodulators, for example, dopamine (531, 692), serotonin (232), and dynorphin (938). Importantly, an increase in intracellular Ca^{2+} is also achieved by OXT itself via OXTR binding and activation of transient receptor potential vanilloid type-2 Ca^{2+} channels (TRPV2). This effect on Ca^{2+} entry, which is phosphoinositide 3-kinase (PI3K)-dependent, has been demonstrated in the PVN but also in primary hypothalamic cells and in rat immortalized H32 cells (see below; Ref. 1044). This mechanism is likely to contribute to the auto-excitatory nature of somato-dendritically released OXT as demonstrated within the SON in the lactating and parturient rat (580, 739; see above).

In addition to extracellular Ca^{2+}, the activation of Ca^{2+} from intracellular stores was also found to be important for somato-dendritic, but not terminal, release of OXT (640, 644, 1010). Activation of somato-dendritic OXTR, e.g., by locally released OXT itself, is sufficient to increase intracellular Ca^{2+} concentrations from thapsigargin-sensitive, but ryanodine-insensitive, intracellular stores (634, 644) and, therefore, to elicit further dendritic OXT exocytosis from large dense-core vesicles. Thus, in contrast to terminal secretion, which is largely dependent on the frequency of action potentials, dendritic release is less tightly coupled to action potentials and not necessarily dependent on the electrical activity of OXT neurons (640, 644).

The transmembrane receptor CD38 has been identified as another essential component for the rise in intracellular Ca^{2+} and OXT secretion (445, 489). Here, CD stands for cluster of differentiation, since each of the CD proteins was originally defined as a blood cell "differentiation antigen" recognized by multiple monoclonal antibodies and found to consist of relatively few groups ("clusters"), each recognizing a single cell-surface protein. So far, >150 CD proteins are known. CD38 can catalyze the formation of second messengers, which are essential for the activation of intracellular Ca^{2+} stores, i.e., of cyclic ADP-ribose and of nicotinic acid adenine dinucleotide phosphate (NAADP) (308, 443). Thus these CD38-dependent cyclic ADP-ribose or NAADP signaling pathways play an essential role in exocytotic processes of neurotransmitters (600) and were also suggested to be important for OXT release from hypothalamic neurons. Based on the findings that, in mice lacking the CD38 gene ($CD38^{-/-}$), OXT secretion into blood was reduced and social behavior skills such as social memory were impaired, Jin et al. (489) hypothesized that CD38 also plays a role in intracerebral OXT release (for review, see Ref. 442). This is further supported by human studies associating single nucleotide polymorphisms (SNPs) in the human CD38 gene with the etiology of autism spectrum disorder (e.g., high-functioning and low-functioning autism) characterized by severe impairment in various aspects of social behavior (for review, see Ref. 444). However, OXT plasma levels were found unchanged in healthy subjects with or without the mutation.

In addition to the above-mentioned factors, cytoskeletal elements are also important for the control of neuronal vesicle release. Here, an actin network proximal to the plasma membrane, usually referred to as cortical F-actin, was described in somata of magnocellular OXT neurons. F-actin appears to regulate the trafficking of functionally mature, release-competent vesicles to fusion sites and is, therefore, likely to be involved in the differential control of OXT release from somata, dendrites, or axonal terminals (for details, see Ref. 640).

4. Intracerebral OXT release in a non-synaptic fashion

Despite the presence of oxytocinergic axons in various brain regions (see **FIGURE 6** and sect. IV*B*), evidence for presynaptic release, as shown in the neurohypophysis, is still missing. Therefore, intracerebral release of OXT was hypothesized to occur non-synaptically, from either axons or axon collaterals of magnocellular PVN (and SON) neurons projecting to forebrain and other limbic regions, as well as from dendrites and somata within the hypothalamic PVN and SON. As such, OXT may rather act as a neuromodulator than as a classical neurotransmitter on nearby and also distant neuronal structures (591, 608, 753).

This view is supported by the spatial distribution of large dense-core vesicles containing OXT, which are not located in the active zones of pre-synapses in the few OXT synapses found in the SON (1002) and ventromedial hypothalamic nucleus (394). Moreover, OXTR could not be attributed to postsynaptic membranes so far. Furthermore, the onset of electrophysiological responses to OXT is delayed, thereby exceeding the time typically needed for synaptic transmission (1–10 ms) and ranging within seconds in the central amygdala (544, 545) or other brain regions. A similar second-range delay of cellular responses was recently demonstrated after evoked somato-dendritic release of AVP from magnocellular PVN neurons, pointing toward a similar non-synaptic, diffusion-like neuropeptide action that allows for inter-populational cross talk within ~100-μm distance (967). However, this view is challenged by the finding that the OXT agonist TGOT depolarized small hilar interneurons in hippocampal slices and facilitated subsequent GABA release not only onto pyramidal cells but also onto mossy cells of the granular layer of the dentate gyrus, as described above (sect. III*B*) (420).

The non-synaptic mode of release should be further confirmed by time-lapse imaging, implementing recently developed techniques for monitoring, docking, and release of

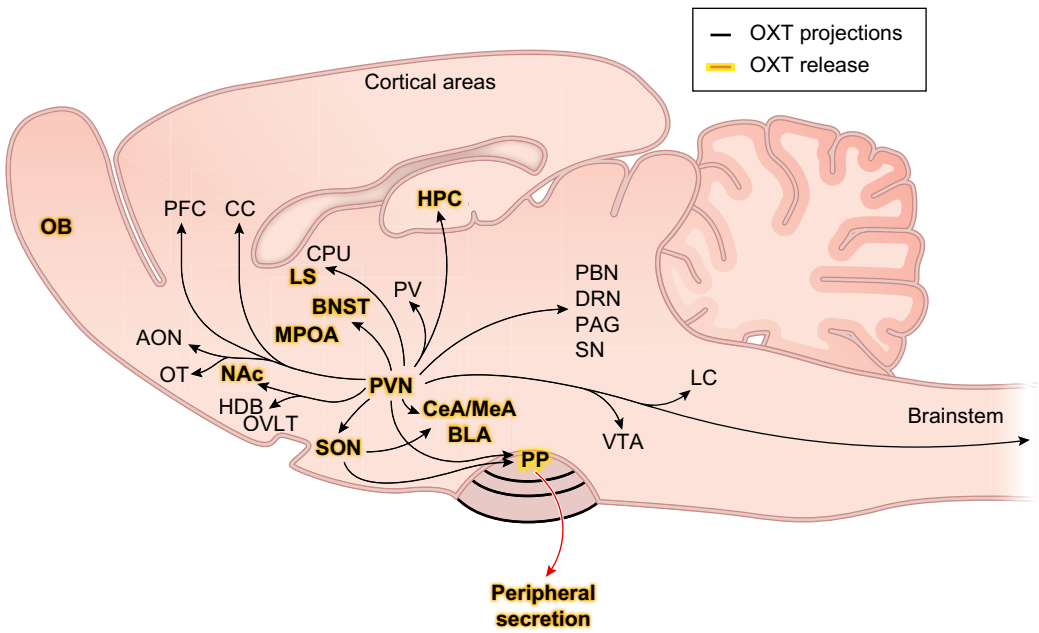


FIGURE 6. Representative anatomical scheme of a rat brain (sagittal slice). OXTergic projections originating from the PVN are depicted as black lines, connecting brain region where OXTR expression has been detected (also see **TABLE 1**). Brain regions where OXT release has directly been shown by microdialysis are highlighted by a red halo. AON, anterior olfactory nucleus; OB, olfactory bulb; OT, olfactory tubercle; Nac, nucleus accumbens; OVLT, organum vasculosum laminae terminalis; SON, supraoptic nucleus; PVN, paraventricular nucleus of the hypothalamus; PP, posterior pituitary; PFC, prefrontal cortex; CC, cingulate cortex; MPOA, medial preoptic area; BNST, bed nucleus of the stria terminalis; LS, lateral septum; CPu, caudate putamen; PV, paraventricular nucleus of the thalamus; CeA, central amygdala; MeA, medial amygdala; BLA, basolateral amygdala; VTA, ventral tegmental area; LC, locus coeruleus; PBN, parabrachial nucleus; DRN, dorsal raphe nucleus; PAG, periaqueductal gray; SN, substantia nigra; HPC, hippocampus; HDB, nucleus of the horizontal limb of the diagonal band.

large dense-cored vesicles (1042). These techniques should also allow dissection of the role of glutamate- or GABA-containing synaptic vesicles in OXT neurons (458), which remain enigmatic since fast synaptic transmission from axons of magnocellular OXT neurons either in the hypothalamus or extrahypothalamic places could not be shown so far (544, 545).

E. Stimuli of OXT Secretion into Blood

OXT concentrations in plasma or other peripheral body fluids reflect the activity of magnocellular OXT neurons projecting to the neurohypophysis only. To assess OXT secretion from the neurohypophysis into blood, OXT concentrations have been quantified mainly in plasma but recently also in saliva and urine under basal and various experimental conditions. There are several advantages and disadvantages of the quantification of OXT in these body fluids **(BOX 2)**. Both physiological as well as pharmacological stimuli have been shown to trigger OXT secretion from neurohypophysial terminals into the blood stream in various mammals, including mice, rats, cows, and humans.

1. Birth

Parturition-related events are classical physiological stimuli triggering OXT secretion into blood, since OXT is a functional part of the so-called Ferguson reflex (326). This neuroendocrine reflex is defined as a self-sustaining positive feed-forward cycle of uterine contractions. Briefly, the Ferguson reflex is initiated by increased pressure on the cervix or vaginal walls, and comprises somato-sensory neurons with synapses in the dorsal horn of the spinal medulla, ascending axonal connections to the brain in the anterolateral columns, and OXT neurons of the hypothalamic SON and PVN with axonal connections to the neurohypophysis. Finally, activation of OXT neurons, which is amplified by locally released OXT-mediated positive feedback (739), results in the secretion of OXT into blood (349, 360, 592), where it promotes further uterine contractions via OXTR, thus further increasing pressure on the cervix. Such secretion into blood was found to be pulsatile in pigs, where it, however, did not correlate with fetal expulsion or abdominal contractions (376). Details of a potential pulsatile secretion of OXT during delivery are not known in other species (see **BOX 4**). The OXTR in the myometrium is upregulated at the end of pregnancy as a result of a functional increase of the estrogen-progesterone ratio (966) (see sect. V). Despite the observation in OXT knockout mice that OXT does not seem to be essential for parturition in this species, pharmacological interference with the OXT system around parturition indicates that increased OXT neuron activity and OXT secretion indeed contribute to the birth process in "normal" mice (284).

BOX 2. Methods and problems to monitor OXT secretion into blood

OXT secretion into blood has been quantified by measuring OXT concentrations mainly in plasma but also in saliva and urine. Plasma samples can be withdrawn in larger quantities and more frequently in larger mammals, including humans, but is rather limited in rats and mice. However, for the reliable detection of physiological levels of plasma OXT in pg amounts, plasma extraction is essential to avoid false-positive results (238, 700). Sampling of saliva (164, 238, 323) or urine (323, 725, 988) has the advantage of being non-invasive and thus stress-free, which is of importance for stress-sensitive experimental designs, for example, in primates or in distinct patient cohorts (e.g., for patients with anxiety disorders or specific phobias, or in children). Furthermore, saliva and urine samples can be collected without professional medical support at home, and an extraction procedure is not needed, since large quantities of high molecular weight proteins are missing (238). However, whereas plasma and salivary OXT have been shown to be correlated (323, 403, 517), plasma and urine OXT concentrations have not (323, 356), making urinary OXT a less reliable measure of peripheral OXT secretion. In addition, the precision of the temporal dynamics of peripheral OXT concentrations needs consideration. The temporal resolution of OXT fluctuations in saliva and urine should rather be limited; in both fluids, OXT concentrations are likely to integrate plasma OXT concentrations over a specific, still unidentified time period. An important methodological problem these days is the use of validated, highly specific detection assays allowing the quantification of physiologically meaningful concentrations in any body fluid (see sect. XIII).

2. Lactation

The other classical stimulus for OXT secretion is suckling in the lactating mammal, with OXT being a functional part of the milk-ejection reflex. Briefly, the suckling stimulus activates pressure-sensitive somato-sensory neurons located in the nipples connected via the spinothalamic tract to the brain, which triggers a burst-like and simultaneous (718) activation of hypothalamic OXT neurons amplified by locally released OXT (581, 740), with the result of pulsatile OXT secretion into the blood stream. Subsequently, circulating OXT binds to OXTR of myoepithelial cells surrounding the milk ducts, which causes the contraction of those cells in the mammary gland and results in increased intraluminal (intramammary) pressure and ejection of milk from the alveolar lumen. The number of OXTR on the myoepithelial cells is upregulated in pregnancy and lactation (965). The detection of the suckling-evoked pulsatile OXT secretion as shown in various mammals including humans (446, 683, 1034) is methodologically challenging and needs frequent blood sampling; in saliva, this pulsatile release pattern cannot be mirrored (237).

3. Mating and sexual stimulation

In both males and females, mating and sexual stimulation have been linked to an increased OXT system activity, as reflected by increased OXT secretion into blood in vari-

ous mammalian species (377, 1064). Also, increased plasma OXT concentrations have been found in sexually aroused men and women during sexual self-stimulation, with peak OXT concentrations found during ejaculation and orgasm, respectively (157, 728). This has recently been confirmed in saliva samples from healthy men and women (237). Whether such release occurs in a pulsatile manner is currently unknown. In estrous ewes, pulsatile release of OXT was found in the presence of a ram, which was, however, independent of coitus (377). It is worth mentioning that OXT concentrations in non-extracted plasma samples were found to be elevated in new lovers (compared with singles) and remained at higher levels within 6 mo, which may suggest generally increased OXT activity during the early stage of romantic attachment (919). Generally, such data have to be considered with caution, since using enzyme assays of unextracted plasma are likely to co-detect substances unlike OXT, thus yielding unreliable data (607) (see sect. XIII).

4. Stress-related stimuli

Exposure to various stressors activates OXT neuronal activity and OXT secretion into blood. Such stressors include physical exercise, socio-emotional stress, and osmotic stress, as mainly studied in rodent species and humans. Thus OXT concentration in plasma was found to be increased in response to forced swimming in male rats and mice, and virgin or pregnant female rats (283, 593, 751, 1017, 1100), but not in virgin female mice (282). Intense emotional stress, such as restraint in rats (509), also increased plasma OXT, whereas acute exposure to a dominant male rat did not measurably increase OXT plasma levels (309).

In humans, OXT concentrations in both plasma and saliva were increased during physical exercise, such as running (237, 584). Moreover, exposure to the Trier Social Stress Test (TSST)—a model of acute psychosocial stress (538)—also resulted in elevated OXT concentrations in plasma and saliva (237, 824). Even rather subtle, positive socio-emotional stimuli, such as intense mother (or father)-infant interactions, as mirrored by the frequency of touching their child, were found to be related to OXT concentrations in saliva and in non-extracted plasma samples (321, 324). Interestingly, even social interspecies interactions between the owner and his/her dog, especially those initiated by the dog's gaze, increased urinary OXT concentrations in both owners and dogs (733, 734).

Hyperosmotic stimulation, i.e., an increase in plasma osmolality, is also relevant for activating the OXT system, resulting in activated neuronal OXT synthesis and secretion into the blood stream (509, 590, 642, 743).

F. Intracerebral OXT Release

The presence of OXT-positive fibers and of OXTR within their brain target regions suggested the local release of endogenous OXT. Such local release finally determines the concentration of a biologically active neuropeptide in the extracellular fluid of a given brain area and allows subsequent local receptor binding. In addition, local enzymatic clearance by peptidases and/or diffusion of OXT via bulk flow contribute to the dynamic alterations in regional OXT concentrations as a consequence of local OXT release.

Our knowledge regarding the stimuli and the dynamics of such intracerebral OXT release mainly derives from intracerebral microperfusion studies performed in rats, rabbits, and sheep, with the initial use of the push-pull perfusion method, which has later been developed into the more sophisticated method of intracerebral microdialysis (see **BOX 3**). Despite the

BOX 3. Methods and problems to monitor OXT release within distinct brain regions

Intracerebral microperfusions are performed within a distinct brain region with the aim to monitor fluctuations of a given substance in the extracellular fluid surrounding the microperfusion device over a given period of time in the freely behaving animal. Both the so-called push-pull perfusion and the more sophisticated microdialysis were shown to be suitable to study the local release of OXT under basal conditions or in response to a physiological, pharmacological, immunological, or environmental stimulus of interest. Intracerebral microdialysis is based on the principle that substances in the extracellular fluid surrounding the small semipermeable dialysis membrane (diameter: 0.2 mm; length between 1 and 4 mm; concentric or U-shaped tip of the microdialysis probe) will diffuse from a higher to a lower concentration, i.e., from the extracellular fluid into the medium of the inner compartment of the dialysis probe. The probe is slowly perfused with either Ringer's solution or artificial cerebrospinal fluid at a speed of 1–3 μl/min. Despite the fact that the preferred pore size of the dialysis membrane should exceed the molecular weight of the substance of interest at least 10- to 20-fold, the relative recovery of substances such as OXT (1,007 Da) from the extracellular fluid in the microdialysate is only ~1.5–3% (79, 616, 782). Consequently, highly sensitive assays for the quantification of OXT concentrations in the $<$1-pg range are needed, despite the fact that nonapeptide concentrations in the extracellular fluid of the SON were found to be 100- to 1,000-fold higher than in plasma (623). To the best of our knowledge, only radioimmunoassays using antibodies with high specificity and sensitivity were routinely used to quantify OXT (and AVP) in microdialysates. Another consequence of the low recovery of OXT by microdialysis is a relatively low temporal resolution, with 20- to 30-min sampling intervals needed to provide reliable quantification of OXT in microdialysates (for details, see Ref. 621). Consequently, OXT content in consecutively sampled microdialysates generally reflects and integrates OXT fluctuations in the extracellular fluid during the sampling period and is interpreted as alterations in local OXT release over this time period. Thus we have to keep in mind that information about the temporal dynamics of local OXT release within selected brain regions cannot be provided in a minute or second range, which would reflect the secretory neuronal activity patterns with higher precision.

BOX 4. Open questions

1) What are the functions of neurophysins after it is co-released with OXT, either from neurohypophysial terminals into blood or after neuronal release within target brain regions?
2) Is there classical synaptic release of OXT from presynaptic structures with actions on OXTR of the postsynaptic membrane within the brain?
3) To which extent does peripherally circulating OXT, i.e., detected in plasma or saliva, reflect OXT release in the brain?
4) Is OXT secreted into blood during labor and delivery in a pulsatile manner, and, if so, what are the clinical implications for OXT treatment during birth to promote labor and to facilitate the birth process?
5) Is there an OXT binding protein in plasma, and what is the potential function of OXT binding to such protein after its neurohypophysial release, or, alternatively, after i.n. application of OXT and uptake into blood in large amounts?
6) What is the functional relevance of SNPs in the OXTR gene, and how do Oxtr polymorphisms affect OXTR-coupled neuronal signaling?
7) What are the physiological and intracellular consequences of a chronically activated OXTR compared with an acute stimulus?
8) What is the half-live of an OXTR expressed in neuronal tissue and its OXT binding?

fact that microdialysis is an invasive approach, a significant contribution of plasma OXT to neuropeptide content in microdialysates is rather unlikely, as has been experimentally shown (741, 744, 890). First, stimulus-induced alterations in OXT content in microdialysates are dependent on the local neuronal activity and can be locally blocked and further enhanced by using hyperpolarizing and depolarizing fluids, respectively (744). Second, repeated iv infusions of OXT during ongoing push-pull perfusion did not elevate OXT content in perfusates (741; but see Ref. 754). Furthermore, within the SON, where excessive neuropeptide release from densely packed dendrites and somata was described (641), it has been roughly estimated that local OXT concentration in the extracellular fluid is ~100- to 1,000-fold higher than in plasma (589), making any contribution of the latter unlikely.

Despite its limitations **(BOX 3)**, microdialysis performed within small and locally restricted brain regions reflects a clear advantage over other attempts to estimate local OXT release. For example, postmortem quantification of regional OXT content after various experimental manipulations has to be interpreted with caution, since OXT content surely reflects both intracellular, i.e., vesicular and neurobiological inactive, neuropeptide, as well as truly released, i.e., neurobiological active peptide. These two forms of local OXT contributing to local peptide content cannot be distinguished from each other in tissue homogenates. In addition, the estimation of (postmortem) peptide content reflects only a static picture of a larger region and cannot reveal the dynamics of release, for example before, during, and after a specific physiological or pharmacological stimulation.

Although the immunohistochemical detection of neuronal OXT protein or quantification of local OXT mRNA by in situ hybridization cannot provide insights into the stimulus-dependent dynamics of local release, these methods provide detailed spatial, i.e., morphological, information regarding OXT synthesis, transport, or storage, even on a single neuronal level and, thus, essentially supplement available data on local release within the brain.

1. Regions of OXT release in the brain

OXT release has been studied within selected brain regions, which were shown *1*) to be innervated by OXT fibers, *2*) to express the OXTR, and/or *3*) to be relevant for OXT-mediated behavioral or physiological effects. Thus OXT release was successfully monitored within various limbic brain regions, including the rat and mouse dorsolateral and ventral septal areas (298, 649, 741, 1148), the rat dorsal hippocampus (590, 741) and central amygdala (297), the nucleus accumbens of voles (100), the substantia nigra, olfactory bulb, bed nucleus of the stria terminalis and medial preoptic area of sheep (517, 520), and within the rat nucleus of the solitary tract (587, 890). OXT released within these central target regions may originate from different neuronal sources: some magnocellular OXT neurons in the hypothalamic PVN and SON, which mainly project to the neurohypophysis, were found to have axon collaterals to central targets (544, 692a). In addition, there exist sparse parvocellular hypothalamic OXT neurons with projections, e.g., to the brain stem (305) or spinal cord (26), involved in the regulation of gastric reflexes, pain, or penile erection. Electrical or optogenetic stimulation of the PVN was described to directly stimulate OXT release within the septum (741, 745), the central amygdala (544), the anterior olfactory cortex (777), and the nucleus of the solitary tract (587), providing additional evidence for the PVN as major source of central OXT.

OXT is also released in substantial amounts within its nuclei of origin, i.e., within the hypothalamic SON and PVN. Using elegant electron-microscopic techniques, Pow and Morris were the first to demonstrate the presence of large dense-cored vesicles as well as omega-shaped fusion profiles at the plasma membrane within dendrites of the SON, implying local dendritic OXT and AVP release (838). At the same time, such somato-dendritic release of OXT within the SON and PVN has been confirmed in vivo by using microdialysis and push-pull perfusion in several laboratories (430, 717, 744, 890).

2. Physiological stimuli of intracerebral OXT release

A major advantage of intracerebral microdialysis is the fact that it can be performed in conscious, freely behaving animals. This allows studying intracerebral OXT release in

response to various physiological stimuli or during a specific behavioral performance, as has been done, for example, in rats, sheep, mice, and voles.

So far, all reproductive stimuli such as birth, suckling in the lactating animal, and mating in males and females, which were all shown to activate OXT secretion into the blood stream (see sect. IV*E*), were also found to trigger OXT release within distinct brain regions. However, only a limited number of brain regions has been studied so far during parturition, suckling, or sexual stimulation (see **TABLE 3**), and increased OXT release has been shown in the hypothalamic PVN and SON, septum, dorsal hippocampus, bed nucleus of the stria terminalis, olfactory bulb, nucleus accumbens, and medial preoptic area (for details see **TABLE 3**; Refs. 520, 717, 741, 743, 773, 885, 1071; for review, see Ref. 591). Such local release in response to reproductive stimuli is region-dependent and stimulus-specific (see **TABLE 3**). An important aspect is the fact that the temporal dynamics of OXT release, e.g., within the hypothalamic SON or PVN, and into blood is likely to differ, which has only been studied in detail during few circumstances (see below).

In addition to reproduction-related stimuli, physical and emotional stress, and osmotic stimulation were found to stimulate the OXT system, since OXT is considered a stress hormone (509). Thus stress-induced intracerebral release of OXT occurs, in most cases, parallel to OXT secretion into blood [but see differences in temporal release patterns within the SON and into the blood in response to ip hypertonic saline (642, 743)]. For example, exposure to 10 min of forced swimming—a combined emotional and physical stressor—seems to be a particularly robust event, which triggers the release of OXT both within the SON and PVN, the central amygdala, as well as into the bloodstream, as studied in male and female rats (297, 1017, 1087, 1100, 1101). Similarly, exposure to 10 min of shaker stress was found to trigger both OXT release within the rat PVN as well as into blood (765) (see **TABLE 3**).

An example for the described region-dependent release of OXT independent of peripheral OXT secretion provides exposure to psycho-social and fear-related stressors, such as social defeat (298). Indeed, in male rats, exposure to a larger and aggressive conspecific (social defeat) selectively stimulated OXT release within the SON and the mediolateral septum, whereas local release within the PVN (and peripheral secretion into blood) was described to remain unchanged (298, 309).

In virgin females, defeat by an aggressive lactating dam represents a strong psychosocial stressor [maternal defeat (758)], resulting in a significant rise in OXT concentration in the extracellular fluid of the PVN, but not within the amygdala or the lateral septum (101). For the lactating resident rat, the defense of her offspring seems also to be stressful, since OXT release within the PVN and the central amygdala was elevated in dams displaying a high level of maternal aggression (102).

It is of interest to note that, in parallel to the activation of central and peripheral OXT release in response to various stressors, stressor exposure also results in a robust activation of the hypothalamo-pituitary-adrenal (HPA) axis and that multiple interactions between the OXT system and the HPA axis exist (see below). With respect to the regulation of intracerebral OXT release, adrenalectomy and loss of circulating corticosterone abolished the swim-induced release of OXT within the PVN, an effect that could be reversed by acute infusion of corticosterone (1017). This indicates that

Table 3. *Examples of stimuli for OXT release in brain and blood*

Stimulus	Species	Brain Region	Plasma OXT	References
Mating	Rat	PVN	Yes	346, 1102
Suckling	Rat	Septum, dorsal hippocampus, SON, PVN	Yes	457, 765, 767
Birth, suckling, eating, separation from lamb	Sheep	Substantia nigra, olfactory bulb, BNST, medial preoptic area	Yes	532, 534, 535
Stress (shaker, forced swim)	Rat	Amygdala, PVN, SON	Yes	299, 791, 1131
Adrenalectomy/corticosterone	rat	PVN	Yes	1049
Social interaction	Rat, mouse	Lateral septum	n.d.	300, 669, 1180
Hyperosmotic stimulation	Rat	Septum, dorsal hippocampus, SON	Yes	607, 662, 767
Electrical or optogenetic stimulation of PVN	Rat	Septum, amygdala, nucleus of the solitary tract	No	561, 604, 769
α-MSH (Melanocortin)	Rat	SON	No	920
Naloxone in morphine-dependence	Rat	SON, septum	Yes	917

Examples of stimuli for OXT release in brain and blood in several species and related publications. n.d., not determined.

factors of the stress axis, most likely glucocorticoids, contribute to stress-induced alterations in OXT neuronal activity and OXT release.

Despite the fact that the sensitivity of monitoring central OXT release patterns by microdialysis is a priori limited, even subtle, largely stress-free social stimuli were found to increase the local concentration of OXT in the extracellular fluid. For example, repeated investigation of same-sex, same weight, or juvenile conspecifics in the home cage stimulated OXT release within the lateral septum of male mice (1148) and rats (649). It seems that specialized OXT pathways even consisting of only a few neuronal connections are activated by subtle social interactions, which in the case of OXT in the dorso-lateral septum are essential for overcoming social fear (1148) and, consequently, for promoting naturally occurring social preference behavior or social memory (647, 649). It is likely that such subtle social stimuli are also capable of activating OXT secretion into blood in small amounts, but whether this occurs in measurable quantities has not been studied yet.

3. Differences in central release and peripheral secretion patterns

Despite the finding of simultaneous or coordinated intracerebral and peripheral release of OXT in response to most physiological stimuli studied so far (see above), it is important to note that the release patterns into the two different compartments have different temporal dynamics. For example, the suckling-induced release of OXT within the SON is likely to precede its secretion into blood during the milk-ejection reflex (717). Similarly, in response to systemic osmotic stimulation by ip administration of hypertonic saline, the temporal dynamics of OXT release into blood and within the brain, and also within different brain regions, was found to differ. Whereas the acute rise in plasma OXT as a result of increased plasma osmolality was accompanied by an acute increase in OXT release within the septum and dorsal hippocampus within 30 min (590), a severely delayed response of OXT release was found from dendrites and perikarya within the SON, which peaked only after several hours (642, 743). This direct comparison of OXT secretion into blood and release within the hypothalamus was only possible by using microdialysis systems designed for either blood or brain (743). However, in most cases, methodological differences between blood sampling (punctual sampling) and sampling of brain microdialysates (over 30 min) do not allow the direct temporal comparison of release patterns into the different body compartments.

In summary, the fine-tuned regulation of local OXT release from OXT neurons within the hypothalamus or from OXT fibers terminating within distinct brain regions and subsequent OXT binding to local OXTR are prerequisites for the adequate behavior of an individual. The patterns of intracerebral release of OXT can be summarized as being strictly region- and stimulus-dependent, and such release can occur in a coordinated manner to OXT secretion into blood or independent of it (544, 591). In any case, differences in temporal dynamics of peripheral secretion and central, regional release patterns exist. Moreover, the different pharmacokinetics in the two compartments have to be taken into account as well. Therefore, plasma OXT can be considered only as a rough indicator of the activity of the brain OXT system (607, 753).

4. Optogenetic and chemogenetic stimulation of brain OXT neurons

The establishment of viral vectors as well as transgenic mice expressing fluorescent reporter proteins, such as Venus, selectively under the control of an *Oxtr* or *Oxt* promoter fragment (305, 441, 544) was already a significant step forward to allow the detailed analysis of OXTR distribution in the brain and of OXT fibers projecting to most of these regions. In 1979, Francis Crick predicted that, to elucidate neuronal codes that specify behavior and perception, "a method (is needed) by which all neurons of just one type could be inactivated, leaving the others more or less unaltered" (211). In the past decade, the development of molecular-genetic tools, such as optogenetics (1132) and chemogenetics (36), allows manipulation of neuronal activity in a highly cell type-specific manner, which has also been utilized to selectively stimulate (or inhibit) OXT neuronal activity and local OXT release.

Optogenetics is a technology that allows fast control of precisely defined terminal release of neurotransmitters or neuromodulators from neurons, which express light-sensitive channelrhodopsin-2 or mutated derivatives of channelrhodopsin-2 or -1 via previous local adenoviral transfection, whose expression is under the control of a distinct promoter, e.g., the OXT promoter. Blue light-stimulation causes cell type-specific control at a millisecond time scale (251). Several studies have utilized optogenetic tools to reveal behavioral or physiological effects of locally released OXT (183, 486, 544, 777, 1107). For example, Knobloch and colleagues (544) showed that high-frequency (50 Hz, blue light) stimulation of channelrhodopsin-2-expressing OXT terminals within the centrolateral amygdala decreased freezing responses in fear-conditioned rats, likely via activation of local GABA neurons.

Xiao and colleagues studied the involvement of mainly parvocellular OXT neurons within the PVN projecting to the ventral tegmental area and substantia nigra in the regulation of midbrain dopamine neurons (1107). Blue light-stimulation of channelrhodopsin-2-expressing OXT neurons facilitated OXT release within the ventral tegmental area and, thus, specifically activated local dopamine neurons. In contrast, within the substantia nigra, optic stimulation of local

OXT release indicated an inhibitory effect on dopamine neurons, which was likely mediated by activation of local OXTR-expressing GABA neurons (1107).

The advent of viral vector-based chemogenetic approaches allows the selective inhibition or activation of neurons expressing **d**esigner **r**eceptors **e**xclusively **a**ctivated by **d**esigner **d**rugs (DREADDs). DREADDs are engineered GPCR, which are activated by otherwise inert small molecules (36). For example, a mutated human muscarinic acetylcholine receptor is activated by the blood brain barrier-permeable molecule clozapine N-oxide (CNO). Although inert under most circumstances and experimental paradigms, CNO can produce behavioral effects when applied alone, which highly emphasizes the necessity of an appropriate no-transfection control group in DREADD experiments (653). Adenoviral-based expression of different classes of DREADD allows neuronal activation and inhibition, respectively. Activation of an excitatory DREADD (hM3Dq) by CNO activates the Gq-mediated signaling and induces increased neuronal firing, a rise in intracellular Ca^{2+} levels, and neurotransmitter release. Such gain-of-function can be achieved in OXT neurons by selective expression of Gq-coupled DREADD under the control of the *Oxt* promoter, which results in elevated intra-PVN somatodendritic and neurohypophysial release of OXT (Grund T, Neumann ID, unpublished observations). Wei and coworkers (1081) have demonstrated that chemogenetic activation of PVN OXT neurons increased the endocannabinoid anandamide content in the nucleus accumbens in an OXTR-dependent manner, indicating chemogenetically induced local OXT release.

In contrast to the gain-of-function studies, loss-of-function analyses are based on Gi-coupled DREADD (hM4Di). In hM4Di-positive neurons, CNO activates inwardly rectifying potassium channels, resulting in neuronal hyperpolarization and silencing neuronal activity (305).

In an elegant study by Eliava and colleagues (305), both loss-of-function (chemogenetic) and gain-of-function (optogenetic) studies have been combined to reveal the capacity of OXT to regulate pain sensitivity. Here, chemogenetic inhibition of parvocellular OXT neurons in the PVN projecting toward the spinal cord decreased the pain threshold and increased pain sensitivity. In contrast, optogenetic stimulation of these neurons exerted the opposite effect; in detail, channelrhodopsin-2 was selectively expressed in a CRE-dependent manner under the control of the OXT promoter in a subpopulation of parvocellular OXT neurons, thus allowing the selective activation of parvocellular PVN OXT neurons projecting toward the spinal cord. Blue light-activation of these OXT neurons in rats repressed nociception and promoted analgesia (305). Also, highly selective chemogenetic inhibition of those OXT neurons expressing DREADD and projecting to the lateral septum of lactating mice prevented the lactation-induced and OXT-dependent lack of social fear (692a). Thus optogenetics and chemogenetics are important methodological developments that, especially when used in combination, allow the detailed study of subpopulations of OXT neurons and their functions in the brain by selective modulation of local OXT release.

5. Interaction of OXT with neuropeptides and neuroactive substances

In addition to the physiological conditions described above, various pharmacological stimuli trigger peripheral as well as intracerebral OXT release. Moreover, OXT release is stimulated by, and OXT interacts with, various other neuropeptides of the brain such as α-melanocyte-stimulating hormone (α-MSH), angiotensin IV, cholecystokinin octapeptide (CCK-8), corticotropin releasing factor (CRF), dopamine, glucocorticoids, leptin, orexin, opioids, prolactin, serotonin, or vasopressin, indicating complex interactions between the multiple neuropeptide systems of the brain, as described in detail below.

A) ALPHA-MSH. The anorexic neuropeptide α-melanocyte-stimulating hormone (α-MSH) is part of the melanocortin family, derives from the Pro-opiomelanocortin (POMC) precursor, and is expressed in melanotroph cells of the intermediate pituitary lobe and in the hypothalamic arcuate nucleus (1080). α-MSH-positive fibers project to various brain areas including the SON (774, 912), where its receptors, melanocortin receptors 3 and 4, are localized (725). Infusion of α-MSH into the brain induced the neuronal expression of the immediate early gene c-Fos in the SON (893). Interestingly, although OXT is released from dendrites or soma of magnocellular neurons within the SON, OXT secretion into blood was found to be inhibited by α-MSH, likely due to inhibition of electrical activity of OXT neurons (893). Thus α-MSH provides an example for a stimulus, which induces an independent release of OXT within the brain and into the blood. As a behavioral consequence of melanocortin receptor 4 agonist (melanotan II or Pf446687) stimulation in adults or early life, brain OXT release is facilitated and leads to enduring partner formation in the adult monogamous prairie voles (57, 705).

B) ANGIOTENSIN IV. It has been generally accepted that the renin-angiotensin-aldosterone system is a cardiovascular hormonal system that impacts on brain regions involved in memory and learning (hippocampus), or regulation of stress and anxiety-like behavior (hypothalamus, amygdala) (79, 674). The effects of angiotensin IV are mediated by binding to the AT (4) receptor (or oxytocinase/insulin-regulated membrane aminopeptidase), a constitutively active metallopeptidase (79), that is expressed mainly in the hypothalamus but also in the hippocampus, amygdala, septum, cortex, and olfactory regions (330). Binding of the ligand to its AT (4) receptor leads to an inhibited degradation, and therefore accumulation, of OXT in the extracellular fluid of

the brain and also in blood (76, 330, 367, 368). Consequently, administration of angiotensin IV leads to anxiolysis (79), increased memory and learning effects (367, 368), and smooth muscle (uterus) contraction (368).

C) CCK-8. Systemic administration of cholecystokinin octapeptide (CCK-8) has been shown to activate magnocellular OXT neurons in the SON and PVN and to stimulate OXT secretion from the rat neurohypophysis into blood (94, 414, 784, 859, 1062). This effect is likely mediated via the vagus nerve and projections from the nucleus of the solitary tract to the hypothalamus (609, 676, 859, 1035). Moreover, CCK-8 immunopositive fibers were identified in the vicinity of OXT neurons (449), CCK-8 coexists with OXT in some hypothalamic magnocellular neurons (673), and there are CCK-8 receptors in the SON (231, 775). Simultaneous microdialysis performed within the hypothalamic SON and the jugular vein of rats using specifically designed microdialysis probes demonstrated that systemic CCK-8 stimulates both release of OXT within the brain and into blood, thus providing an example for coordinated and simultaneous release of OXT into both compartments (742). In line with a local role of CCK-8 in neuroendocrine regulation and in support of local CCK-8 receptors, CCK-8 stimulates local OXT release when directly applied into the SON via reversed microdialysis (retrodialysis) (742).

D) CORTICOTROPIN RELEASING FACTOR. One important step toward a better understanding of the interplay between neuropeptides is to characterize the transcriptome of OXTergic neurons. Such analyses revealed that the majority of parvocellular OXT-producing neurons in the PVN co-express CRF and are glutamatergic. In contrast, most OXTergic magnocellular neurons are non-CRF, but CRF receptor 2-expressing glutamatergic neurons as revealed by single-cell RT-PCR and in situ hybridization (29, 221). A small number of magnocellular OXT neurons co-express CRF, the CRFR2, OXTR, and the V1b receptor. Moreover, none of the OXT neurons in the PVN are GABAergic, as indicated by VGLUT2 expression and lack of GAD67 expression (220, 221).

In support of interactions between OXT and CRF, we could provide evidence for a direct inhibitory effect of OXT on stimulated CRF gene expression in the PVN of rats and mice, and in hypothalamic neuronal cell lines and human neuroblastoma cells expressing the OXTR (499). This data is corroborated by a study that showed a decrease in restraint stress-induced CRF mRNA levels in the PVN by a chronic dose of OXT (10 ng/h for 7 days) in female ovariectomized rats (1094). Studies in voles and rats showed that the inhibitory effect of OXT on CRF mRNA levels might be mediated via GABAergic interneurons (131, 956). The diminished CRF expression via GABAa receptors contributes to postpartum suppression of anxiety-like behavior in rodent dams (630). Vice versa, the CRF system also modulates central OXT release as indicated by pharmacological manipulation. In detail, icv administration of the CRFR2 agonist stresscopin and the CRFR2 antagonist astressin-2B reduced and increased OXT release, respectively, within the nucleus accumbens of male prairie voles (100).

E) DOPAMINE. In addition to the well-described meso-limbic and nigro-striatal dopamine systems of the brain, the incerto-hypothalamic system has been described as a diencephalic region located at the junction of the medial hypothalamus and zona incerta (129, 622, 944). In the hypothalamus, dopamine is mainly expressed in neurons of the so-called dopamine A14 cell group (225), which arborize extensively and innervate other nuclei, such as the medial preoptic area, ventral tegmental area, and PVN (622, 688). In rats, OXTergic and dopaminergic fibers often exist in close apposition to each other (129), with dopamine D2 receptors being expressed directly on OXT neurons (61), suggesting a close interaction between OXT and dopamine systems (62).

OXT has also been implicated in regulating the activity of mesolimbic dopamine pathways during rewarding social interactions (see sect. VIII) and drug addiction and withdrawal (62, 551, 682, 907; sect. XI).

Rat mothers that show a high amount of licking and grooming toward the offspring have higher levels of OXT in the medial preoptic area and PVN, and increased projections of OXT-positive neurons from the medial preoptic area and PVN to the ventral tegmental area. Direct infusion of OXT into the ventral tegmental area increased the dopamine level in the nucleus accumbens (926). This study provided a direct link between OXT and dopamine release within the mesocorticolimbic dopamine system and is consistent with previous reports on OXT-dopamine interactions in the establishment and maintenance of social bonds (Refs. 170, 808; sect. VIIIC). In addition, sexual activity is accompanied by activation of dopamine D2 and D4 receptors in the PVN, which induce the release of OXT in the ventral tegmental area. This OXT release then stimulates the dopaminergic neurons projecting to the nucleus accumbens to mediate the rewarding effect of sexual activity (688, 979).

In humans, dysregulation of dopaminergic signaling is known to be involved in various neuropsychiatric and neurological disorders including autism, Parkinson disease, and depression (62). For instance, some patients with dopamine-dependent disorders (e.g., Parkinson disease or schizophrenia) show disturbances in peripheral (plasma) and central (CSF) OXT levels, and a decreased number of OXT immunoreactive neurons (in postmortem tissue) in the hypothalamus compared with healthy control subjects (845).

F) GLUCOCORTICOIDS. There is a well-described bi-directional link between the OXT system and glucocorticoids, with OXT regulating the activity of the hypothalamo-pituitary-adrenal (HPA) axis mainly at the level of the hypothalamus (see sect. VIII*E*), and with glucocorticoids modulating the OXT system (378, 618). The link between the OXT and glucocorticoid system is supported by the detection of glucocorticoid and mineralocorticoid receptor expression in OXT neurons of the SON and PVN (265, 417). Subcutaneous OXT administration decreased glucocorticoid receptor expression in the CA1+2 fields of the hippocampus (818) and decreased plasma corticosterone levels in female rats (817).

The bidirectional link, on the one hand, also comprises facilitating effects of acute systemic administration of glucocorticoids (corticosterone) in supraphysiological concentrations (25 mg/kg ip) on peripheral OXT release (196) and increased hippocampal OXTR binding in male rats (617, 618). In addition, chronic administration of dexamethasone increased OXTR binding in the bed nucleus of the stria terminalis, lateral septum, and amygdala (804). Also, in the PVN, glucocorticoids were found to induce the release of retrograde messengers, such as endocannabinoids, that suppress the presynaptic release of glutamate via activation of CB1 receptors on presynaptic glutamate terminals (994). Moreover, glucocorticoids rapidly facilitate the release of GABA selectively to magnocellular, but not parvocellular, PVN cells. The suppression of excitatory synaptic inputs in combination with the facilitation of inhibitory inputs to magnocellular PVN OXT and AVP neurons should result in a strong inhibition of PVN outputs (for review, see Ref. 993).

On the other hand, lack of glucocorticoids by adrenalectomy decreased hippocampal OXTR binding in male rats (617, 618) and abolished swim stress-induced OXT release within the PVN (1017). In response to restraint stress, however, increased activation of PVN OXT neurons was detected (578).

In the periphery, adrenalectomy caused an exaggerated secretion of OXT into blood in response to forced swimming (1017) and hemorrhage (229).

In conclusion, chronic absence of glucocorticoids seems to stimulate stress-induced peripheral OXT secretion, indicating an inhibitory effect of glucocorticoids on OXT secretion into blood during the stress response. In contrast, the stress-induced rise in corticosterone seems essential for the release of OXT within the PVN.

G) LEPTIN. Body weight and fat mass are regulated by the adipocyte-derived hormone leptin and various players of the gut system (see sect. X). A recent study demonstrated that icv administration of leptin activates STAT3 phosphorylation in OXT neurons of the PVN and that this activation occurs in a subpopulation of OXT neurons that innervates the nucleus of the solitary tract (813). In addition, increased electrical activity of SON OXT neurons was detected after ip injections of leptin (1059), which is, at least partially, in contrast to the finding that the CCK-8-induced release of OXT within the PVN was reduced by icv-infused leptin (574). The authors speculated that this is due to a reduced CCK-induced noradrenergic neurotransmission, a view that might be challenged by the finding that OXT and noradrenalin act synergistically to stimulate GnRH release from hypothalamic explants (924).

H) OPIOIDS. The effects of opiates and (endogenous) opioids on the OXT system have been studied in great detail. Opioid receptors, i.e., mu- and kappa- but not delta-opioid receptors, are expressed in OXT neurons (980), indicating that these effects may occur at the level of hypothalamic magnocellular neurons, including pre-synaptic inhibition of their afferent inputs as well as pituitary terminals (for review, see Ref. 123). Although there is the general assumption that endogenous opioids inhibit the electrical and secretory activity of OXT neurons as mainly studied in the SON (123), the effects were found to be dependent on the physiological status of the animal. For example, basal OXT release both into blood and within the hypothalamus is strongly inhibited by endogenous opioids, but only in pregnant and not in virgin rats (285). Similarly, the swim stress-induced OXT release within the hypothalamic PVN and SON was found to be inhibited in pregnant rats, as revealed by sc application of the opioid antagonist naloxone, whereas in virgins, endogenous opioids seem to further activate OXT release within the PVN (without effect in the SON) (1087). Thus the activity of OXT neurons is efficiently restrained by endogenous opioids, but only in pregnancy until shortly before birth, and this inhibitory effect is mediated by mu-receptors on the cell body, allowing neuronal, specifically terminal accumulation of OXT until it is needed during the delivery process (123) and the onset of maternal behavior.

Strong effects of opiates on the OXT system have also been revealed in rats made morphine-dependent by chronic icv infusion of morphine over 5 days. Peripheral application of the opioid antagonist naloxone triggered withdrawal symptoms accompanied by a huge excitation of OXT neurons in the SON and, consequently, secretion of OXT into blood in supraphysiological amounts (81, 122, 890). The latter was accompanied by increased intracerebral OXT release specifically within the hypothalamic SON and the septum, but not the hippocampus (890).

I) OREXINS. The neuropeptides orexin-A and orexin-B (also called hypocretin 1/2) are expressed in the lateral hypothalamus and act as neuromodulators of the brain to regulate various functions, including satiety (1041), sleep-wake

rhythm, anxiety (526), and contextual fear conditioning (1076). Orexins were found to primarily inhibit OXT release from neurohypophysial cultures (776) and also within the PVN (655). The mode of action of orexin on a cellular level includes *1*) a primary reinforcing effect on GABA release (72, 478, 797) and *2*) a later secondary inhibitory effect. This inhibitory effect includes the phosphorylation of the $GABA_A$ receptor β_1 subunit by protein kinase C (PKC) and Ca^{2+}/calmodulin-dependent kinase II (CaMKII) (897), thereby leading to a reinforced depolarizing effect on OXTergic neurons. This secondary effect also includes an increase of the astroglial expression of the glutamate transporter GLT-1 via ERK1/2 and PKC activation (934). The primary negative and secondary positive orchestration of OXT release by orexin/GABA is most likely responsible for the regulation of the sleep/wake rhythm (655).

J) PROLACTIN. The prolactin and OXT systems share many features. Prolactin, the hormone important for lactogenesis, is not only synthesized in lactotroph cell of the adenohypophysis but also within the brain (307), specifically within the hypothalamic PVN and SON (1016, 1019). As seen for OXT (see below), prolactin is involved in the regulation of lactation, maternal and sexual behavior, and food intake (118, 286), attenuates the stress responses, and exerts anxiolytic actions (1019, 1020) (for review, see Ref. 1014). In addition, in lactation, the neuronal expression of prolactin and its receptors is strongly activated (1019), and prolactin release within the rat PVN and the medial preoptic area was found in response to suckling (1015). Indeed, interactions between OXT and prolactin, especially at hypothalamic level, are likely to occur. In fact, in virgin rats, acute central infusion of prolactin inhibited the activity of OXT neurons in virgin rats, but this effect was lost, or at least partially reversed, in lactation. Consequently, prolactin may contribute to the high activity of OXT neurons peripartum, since it was found to increase hypothalamic OXT expression (43). In support, icv prolactin chronically infused via osmotic minipumps over 7 days in ovariectomized female rats increased plasma OXT (and AVP), and stimulated c-Fos and OXT mRNA expression within the SON, but not PVN, under basal conditions. This indicates that prolactin contributes to the high OXT system activity peripartum. Moreover, chronic prolactin inhibited the stress-induced OXT secretion into blood (281), and thus prolactin may also be important for the attenuation of stress-induced secretion of OXT found in lactation (751).

K) SEROTONIN. The interplay between the OXT and serotonin systems orchestrates the body's stress response. For instance, stressor-induced OXT release from hypothalamic PVN cells has been blocked by icv administration of a 5-HT antagonist (497). Later studies found that, in addition to the regulation of OXT in the hypothalamus, expression and release of OXT from neurohypophysial tissue cultures was also increased by serotonin (measured in cell culture supernatant by tandem mass spectrometry and radioimmunoassay) (365). This result was surprising insofar as the neurohypophysis was considered responsible for the storage and secretion, not production, of OXT. Contrary to serotonin-induced neurohypophysial OXT secretion, OXTR expression on serotonergic cells in the raphe nuclei indicated a stimulatory role for OXT in serotonin release. Indeed, local infusions of OXT stimulated serotonin release within the median raphe nucleus and reduced anxiety-like behavior (1116). However, site-specific conditional knockout of the OXTR on serotonergic neurons of the raphe nucleus did not result in increased anxiety-like behavior, nor in alterations of female maternal aggression, but reduced intruder-directed aggression of male resident mice (795). Moreover, activation of the 5-HT1B receptor by a specific receptor agonist induced autism-like symptoms, i.e., reduced sociability, reduced preference for social novelty, and reduced rearing in mice. These serotonin-induced autism-like symptoms could be reversed by OXT treatment (595).

L) VASOPRESSIN. Neither magno- nor parvocellular AVP neurons in the PVN co-express OXT. However, parvo- as well as magnocellular OXT neurons express the V1b receptor, which allows them to react to locally released AVP (221). Moreover, vasopressinergic neurons can express the OXTR (221), suggesting strong interactions between the OXT and AVP systems at hypothalamic level. Although AVP effects on OXT functions are less known, OXT regulates somatodendritic as well as peripheral release of AVP in dependence on the activity conditions. Within the SON, OXT inhibited the local release of AVP in response to swim stress, without affecting basal somato-dendritic AVP release. In contrast, local OXTR-mediated actions inhibited AVP secretion into blood under basal conditions but did not contribute to the inhibition of peripheral AVP in response to stress, as revealed by bilateral retrodialysis of an OXT receptor antagonist (OXTR-A) into the SON during ongoing microdialysis and blood sampling (756). Similarly, within the PVN, bilateral administration of the OXTR-A further increased local AVP release in response to swim stress, without affecting peripheral AVP secretion either under basal or stress conditions (756). Electrophysiological recordings suggest that OXT acts predominantly on OXT neurons in an autocrine/paracrine manner, but not on vasopressinergic neurons in the PVN or SON (178, 391, 468, 715). Whether AVP affects OXT neuronal activity or OXT release via actions on the described V1a receptors on OXT neurons remains to be elucidated.

V. REGULATION OF OXTR EXPRESSION AND FUNCTIONING

For a functional OXT-OXTR system, stimulus-dependent expression and release of OXT have to be balanced with a fine-tuned regulation of local OXTR expression. The cell-specific expression of the OXTR in brain tissue necessitates

a strict spatial and temporal transcriptional control, which is brought about either by genetic, i.e., transcription factor-based, mechanisms, by epigenetic modifications of DNA or histones, or on a translational level by non-coding microRNAs as described in detail below. A further, newly discovered transcriptional control is the allele-specific expression of the *Oxtr* gene, which occurs independent of genomic imprinting or genetics but is rather developmental stage and cell type-specific (461).

A. Random Allelic Expression of the *Oxtr* Gene

Using genome-wide analysis of single neurons from the dorsal raphe nucleus or arcuate hypothalamus of the neonatal mouse brain, a random distribution of paternally or maternally expressed OXTR was discovered. If the *Oxtr* gene is indeed randomly expressed from either the maternal or the paternal allele, monoallelic SNPs will consequently result in a mosaic-like *Oxtr* expression in the brain, with potential consequences for associated mental illnesses (461). This random allelic effect was not only detected in mouse brains but also in the dorsal raphe nucleus of cynomolgus macaques, which strengthens the translational aspect of this study and the potential impact it has for human autism, schizophrenia, or general anxiety studies (461).

B. Transcriptional Control of the *Oxtr*

1. The OXTR gene and regulating transcription factors

A human *OXTR* cDNA construct has first been cloned in *Xenopus* oocytes with mRNA isolated from myometrial tissue by Kimura (535). Later, the exact *Oxtr* gene structure has been described for other species, including humans (470), rats (889), mice (571), cows (63), pigs (386), sheep (871), rhesus monkeys (901), and voles (1119) (for the exact human sequence of the promoter and the gene, see Ref. 470). In humans, the mRNA transcript is 3.6 kb long in breast tissue, and 4.4 kb in the ovary, uterine, endometrium, and myometrium. The heterogeneity of the transcript length is, at least in rats, explained by the alternative use of different polyadenylation sites in the 3′ untranslated region (889). The *Oxtr* gene is located on *chromosome 3* (3p25–3p26x·2) as a 17-kb single-copy gene consisting of four exons and three introns (534, 535). The promoter region of the *Oxtr* gene comprises species-dependent subsets of transcription factor binding sites, implying variations among animals and humans. Common transcription factor binding sites in the rodent and human *Oxtr* promoter are SP1, TATA-like motif, an inverted GATA-1 motif, ERE (half or full), c-Myb binding domain, 11 CCAAT/enhancer binding protein β (C/EBP) sites, AP-1/2 sites, and 3 nuclear factor kappa B (NF-κB) binding sites (1000; for review, see Ref. 87). The exact nature of the extracellular signals that activate these responsive elements is not known, although recent publications could show that mechanical stretch of the myometrial cells during labor (1001) as well as labor-induced interleukin-β release increased *Oxtr* mRNA via activated NF-κB and C/EBP-β (1000). In addition, cAMP-activated PKA seems to inhibit transcription of the *Oxtr* gene, a permanent process that is suppressed during the onset of labor, which consequently leads to an increase of *Oxtr* mRNA in myometrial cells (1127).

2. Estrogens

One extracellular signal that regulates the *Oxtr* expression is estrogen. The estrogen receptor (ER) contains an NH_2-terminal DNA binding domain and a COOH-terminal ligand binding domain, and is localized in the nucleus, cytoplasm, and mitochondria. The two ER subtypes differentially affect *Oxtr* and *Oxt* expression: ERα is essential for the induction of *Oxtr* expression but not for maintenance of basal levels, whereas the activated ERβ induces *Oxt* transcription in the mouse brain (186, 929, 1122). Upon binding to 17β-estradiol or related ligands, ER form homo- or hetero-dimers that interact with estrogen response elements (ERE) in the promoters of target genes to activate transcription. Mice and rats, but not humans, carry a complete ERE in their *Oxtr* promoter. In rats, estrogen stimulation only increases *Oxtr* mRNA in estrogen-sensitive regions, such as the hypothalamus, but not in the subiculum or the olfactory nuclei (115, 849). The mechanism underlying this tissue-specific expression is potentially rooted in *1*) regulatory noncoding regions of the *Oxtr* transcript that are differentially expressed due to alternative polyadenylation sites (114) and *2*) tissue-specific methylation of the *Oxtr* promoter (see sect. V*B*). The lack of a complete ERE in the human *Oxtr* promoter does not necessarily exclude any influence of estrogen on the expression of *Oxtr*, since ERα and ERβ can act independently of the ERE and trigger G-protein-coupled signaling cascades to activate transcription factors that have binding sites in the *Oxtr* promoter (614).

3. Progesterone

In general, there is limited evidence for a role of progesterone in the regulation of *Oxtr* expression. Progesterone, which is mainly synthesized in the corpus luteum, adrenals, brain, and, during pregnancy, placenta, helps to maintain uterine quiescence during pregnancy and is, therefore, in clinical use to prevent preterm birth. Progesterone exists in two major isoforms, progesterone A and progesterone B, with the latter being the long form of progesterone, whereas progesterone A is truncated and mainly acts as transactivation repressor of progesterone B (533). In human myometrium samples, the progesterone A-to-progesterone B ratio correlates with the level of *OXTR* mRNA, indicating a

transcriptional regulation of *OXTR* by progesterone B. On a behavioral level, progesterone induces female mating behavior within a time frame of 30 min via the expression of *Oxtr* in the posterior ventromedial hypothalamus (922).

4. Oxtr *promoter methylation*

The molecular basis for tissue-specific expression of the *Oxtr* gene has long been puzzling to researchers. One mode of transcriptional regulation depends on the level of DNA methylation of specific cytosines (CpG sites) in the promoter of the *Oxtr* (534, 664), since DNA methylation reduces the accessibility of the *Oxtr* promoter for transcription factors. An inverse relationship between promoter methylation and *Oxtr* mRNA levels was found in human liver and myometrium (573), murine hypothalamic, and myometrial cells, as well as in the medial amygdala, cerebral cortex, ventromedial hypothalamus, olfactory bulb, and cerebellum of the mouse brain (424). Recently, functional coupling of the amygdala to regions associated with emotion regulation (insular, cingulate, or orbitofrontal cortex), as revealed by fMRI, was found to be inversely correlated with methylation levels of the *OXTR* gene in blood cells (843), suggesting that methylation of the *OXTR* promoter is also associated with *OXTR* expression and binding in the brain and, consequently, with altered emotion processing. In line with this data, methylation of the *OXTR* gene in human blood samples was lower in social anxiety disorder patients (1145). An increased DNA methylation pattern of the *OXTR* was also found in mouth epithelial cells in saliva of depressed women (168). However, in considering these association studies, we have to keep in mind that it is still elusive whether human blood or saliva cells reliably mirror processes in the human brain. One first attempt to approach this question was the study by Beery (66), in which researchers compared maternal care-induced alterations in *Oxtr* promoter methylation in blood cells and regional brain tissue. The offspring of mothers who showed less intense maternal behavior (low licking and grooming) showed lower levels of *Oxtr* methylation, whereas the offspring of high licking and grooming mothers had higher levels of *Oxtr* promoter methylation. However, there was no correlation between striatal or hypothalamic *Oxtr* methylation and *Oxtr* methylation of blood cells; only hippocampal cells showed a modest correlation of methylation with blood cells, indicating no or only weak predictive power for individual *Oxtr* methylation patterns between different tissues (66).

C. Control of the Oxtr Expression by micro-RNAs

Besides the classical regulation by transcription factors, micro-RNAs, i.e., small non-coding RNAs, have also been shown to regulate OXTR synthesis on a transcriptional and translational level (184, 860). The miR-200 family of regulatory micro-RNAs was found to be increased at term and can be induced by progesterone withdrawal by antiprogestin treatment in human myometrial cells. This family of micro-RNAs is known to interact with transcriptional repressors, namely ZEB1 and ZEB2, which in turn inhibit the expression of the *Oxtr* (860). Moreover, in the prefrontal cortex of postmortem tissue of ASD patients, miRNAs that target the *OXTR* gene were upregulated, indicating a regulatory role for miRNAs in OXTR expression in these patients. However, direct empirical proof is still missing (719). As potential feedback loop, OXT treatment also leads to the induction of micro-RNA expression in human myometrial cells and in myometrial tissue taken from women at term before or after the onset of labor, indicating a critical role for OXT as a central regulator of myometrial gene transcription and translation during pregnancy and labor (203).

D. Regulation of *Oxtr* Expression by Ligand Availability

It is general knowledge that pharmacologically increased ligand availability over longer periods can result in receptor downregulation causing paradoxical effects (201, 378). There is, however, limited evidence for such a link between OXT concentrations, for example, within the extracellular fluid of specific brain regions or in plasma, and local *Oxtr* expression. In a mouse model of social fear, reduced OXT release within the lateral septum was accompanied by increased OXTR binding (1148). Pharmacological approaches revealed that chronic icv application of 10 ng/h OXT over 14 days, or repeated intranasal (i.n.) administration of OXT in mice led to downregulation of OXTR binding in a number of brain regions, including the dorso- and ventrolateral septum, basolateral and medial amygdala, and median raphe nucleus, associated with increased anxiety levels (460, 815). In contrast, in OXT knockout mice, the expression of the *Oxtr* in the hippocampus was reduced (1146).

In general, local OXT availability is likely to be dependent *1*) on the regulation of local OXT release and *2*) on enzymatic degradation of OXT. The half-life of OXT in blood plasma is ~3–6 min, whereas in the brain CSF it was found to be enzymatically degraded 20 min after an icv application (693, 892). The enzymatic cleavage by the oxytocinase placental amino peptidase (P-LAP) regulates the OXT availability not only in uterus, placenta, and plasma, but also in the brain. For instance, during pregnancy, P-LAP expression was reported to be upregulated in the hypothalamus (1009), and the oxytocinase L-cystine aminopeptidase (CAP) was elevated in blood (406), presumably to reduce the risk of preterm labor.

E. OXTR Ligand Binding Affinity

Although only one type of OXTR exists, with variants in some species (356), it can occur in a high- or low-affinity

state. Two essential components were described to determine whether the OXTR displays the high-affinity (K_d < 1–5 nM) or the low-affinity state (K_d > 100 nM): *1*) divalent cations, such as Mg^{2+} or Mn^{2+}, and *2*) cholesterol (378, 1086). The conversion of the two affinity states is reversible. Cholesterol seems to stabilize the OXTR for agonists in a high-affinity state and acts, similar to divalent cations, as an allosteric modulator (1086). Cholesterol occurs mainly in specialized regions of the plasma membrane, termed lipid rafts. OXTR that are anchored outside of these cholesterol-enriched domains inhibit cell proliferation via the epidermal growth factor receptor (EGFR) and ERK1/2 activation in a $G\alpha_i$-, PLC-, and PI3-kinase-dependent way, whereas activated receptors that are located within lipid rafts induce cell proliferation via EGFR and ERK1/2, but in a $G\alpha_i$-, PLC-, and PI3K-independent mechanism (863). Whether these different affinity states are the cause for differential neuronal signaling and, therefore, altered behavioral responses to different OXT concentrations is unknown but has to be considered for the application of OXT in humans and animals.

In humans, the promiscuous binding of the natural ligand OXT to the OXTR (K_i = 0.79 nM) and the AVP receptors V1a (K_i = 120 nM), V1b (K_i = 1,782 nM), and V2 (K_i = 1,544 nM), as well as the binding of AVP to the OXTR (K_i = 48 nM) (11) hampers research addressing the effects of exclusive OXTR activation by OXT, leading to the synthesis of over 1,000 peptides and some non-peptidergic compounds that have been tested for their selectivity and potency toward the OXTR (137). Available OXTR agonists and antagonists have been described and reviewed extensively by M. Manning and B. Chini (137, 138, 140, 179, 180, 667–669, 803). By genetically fusing parts of the OXTR with the related V2 receptor, the most important receptor binding domains for OXT were identified: the first three extracellular receptor loops were most important for OXT binding and selectivity. The NH_2-terminal domain and the first extracellular loop of the OXTR interact with the linear amidated COOH-terminal tripeptidic part of OXT (834). The second extracellular loop of the OXTR interacts with the cyclic part of the OXT peptide. Furthermore, the *transmembrane helices 1*, *2*, and *7* were not involved in OXT binding but in binding of the OXTR antagonist d(CH2)5[Tyr(Me)2,Thr4,Orn8,Tyr9]-vasotocin **(FIGURE 7)**.

1. Synthetic OXT receptor agonists

A) TGOT. [Thr^4,Gly^7]-OXT (TGOT) is the only highly selective (selectivity ratio OXTR/V1a > 16.600) and potent OXTR agonist in rats and mice to date (137, 636; **TABLE 4**). Interestingly, the observed selectivity of TGOT for the mouse OXTR in vitro (cell culture) was partially lost when tested in vivo in OXTR knockout or heterozygous mice (898, 899). The relevance and usefulness of TGOT for electrophysiological recordings has been proven in numerous studies (116, 217, 420, 462, 1067, 1068).

The behavioral relevance of exclusive OXTR activation by TGOT has been addressed using Long Evans rats that have been treated with acute synthetic OXT or TGOT during

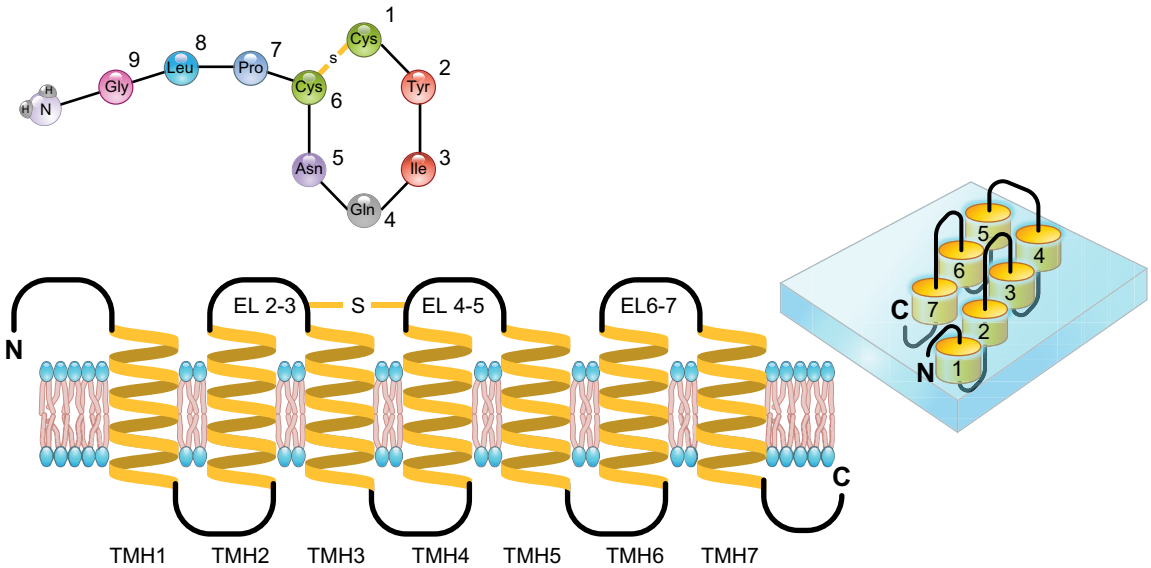


FIGURE 7. *A*: schematic representation of the OXT and OXTR structure. OXT is a nonapeptide molecule with a tripeptide linear part with an amidated COOH terminus, and a cyclic part that is connected via a disulfide bridge between the two cysteines. The OXTR is a seven-transmembrane helix (TMH1–7) receptor with three extracellular loops (2–7) and three intracellular loops (1–6). *B*: three-dimensional representation of the OXTR within the cell membrane. The binding pocket for the OXTR antagonist d(CH2)5[Tyr(Me)2,Thr4,Orn8,Tyr9]-vasotocin lies between the TMH 1, 2, and 7, whereas the OXT binding site comprises the NH_2-terminal region as well as the extracellular loops 2–3 and 4–5.

Table 4. *K_i values for OXT and the OXTR agonists*

Ligand	K_i ± SD, nM					
	Human OXTR	Human V1a	Rat OXTR	Rat V1a	Porcine OXTR	Porcine V2
OXT	0.79 ± 0.22	210 ± 21	1.0 ± 0.1	845 ± 99	0.7 ± 0.2	310 ± 70
TGOT	6.62 ± 1.22	305 ± 85.1	0.8 ± 0.2	>10.000	n.d.	n.d.
Atosiban	11 ± 0.7	0.15 ± 0.02	32 ± 5.0	310 ± 14	52 ± 16	360 ± 90
Carbetocin	7	7.24	1.96	7.24	7.1 ± 0.2	5680 ± 1410
WAY 267,464	58.4 ± 11.3	73	978 ± 71	113 ± 32	n.d.	n.d.

K_i values for OXT and the OXTR agonists TGOT, Atosiban, Carbetocin, and WAY 267,464 in dependence of species and receptor subtype. Table data are from Refs. 180, 383, 633, 689.

adolescence. The OXT-treated rats showed increased plasma OXT levels and increased social behavior in adulthood, whereas TGOT did not change the social behavior in adulthood (982). These results suggest co-stimulatory effect of OXT on the OXTR and AVP receptors in OXT-mediated behavioral effects, rendering TGOT as a useful control in electrophysiological recordings but of limited behavioral use.

In humans, TGOT displays a comparable selectivity for the OXTR as the natural ligand OXT (179), providing no advantage over synthetic OXT for clinical use in humans.

B) ATOSIBAN. Atosiban (1-deamino[D-Tyr(Et)^2,Thr^1]OVT), another synthetic OXTR ligand, has been shown to be a functionally selective, or "biased agonist," since it acts as agonist for the inhibitory Gαi-protein-coupled OXTR, but as antagonist for Gαq OXTR and V1a receptors in kidney and prostate cancer cells (human and canine) (864). Atosiban shows a sevenfold higher affinity for the OXTR than for the V2 receptor in mice (137). This biased activation does not lead to desensitization or internalization of the OXTR, as it is described after OXT, but to persistent ERK1/2 phosphorylation and cell growth inhibition (864; see sect. V*I*).

C) DNALOVT. DNalOVT is a peptidergic biased OXTR agonist that activates only G_{i1} or G_{i3}, but not the OXTR-G_q pathway or the OXTR-G_{i2}, -G_{i3}, -G_{oA}, and -G_{oB} complexes. It also does not induce recruitment of β-arrestin and receptor internalization, or rendering atosiban and DNalOVT, two ligands that are able to differentiate between individual $G_{i/o}$ family members (140).

D) CARBETOCIN. Carbetocin (Ferring Pharm.), also known as deamino-1-monocarba-(2-*O*-methyltyrosine)-OXT has been synthesized by deaminating the NH_2 terminus of OXT and by replacing the disulphide (S-S) bridge between Cys 1–6 with a CH2-S bond that connects a butyric acid group at the NH_2 terminus and Cys 5. This modified peptide OXT agonist is protected from enzymatic cleavage (59), thus increasing its half-life in the peripheral circulation (carbetocin 85–100 min vs. OXT 3–4 min) (369). It has been shown to induce milk let-down and to increase intramammary pressure (205) in lactating sows as well as porcine and human uterine contractions in vivo and in vitro (22, 206). Administration of icv carbetocin reduced anxiety-like behavior (660) and reduced immobility, as well as increased swimming in the forced swim test (174). On a molecular level, carbetocin acts as a functional selective OXTR agonist that is specific for the Gq pathway, most likely acting as V1a and V1b receptor antagonist, and leads to β-arrestin-independent internalization of the activated OXTR (see sect. V*F*; Refs. 379, 803).

E) WAY 267,464. This compound is a non-peptide OXTR agonist with weak rat OXTR affinity and even higher affinity for the rat V1a receptor (440). However, application of WAY 267,464 (Wyeth) to stably expressing OXTR HEK293 cells exerted no functional response at the V1a, but a weak response at the OXTR (EC_{50} = 881 nM). This renders WAY 267,464 as a weak OXTR agonist and potential V1a antagonist. Adult male rats, treated with 100 mg/kg ip WAY267,464, showed impaired locomotion, similar to rats that have been treated with 1 mg/kg OXT (440).

2. Synthetic OXT receptor antagonists

A) DES-GLY-NH_2-D$(CH_2)_5$[TYR(ME)^{2}THR^4]-OVT. This peptidergic selective OXTR antagonist, also referred to as "Inga's compound," has been synthesized by M. Manning (667) and used in behavioral and neuroendocrinological studies to selectively block OXTR-mediated effects of endogenous OXT in the SON (739, 740), PVN (752, 757), septum (298), or central amygdala (297), and also in a human neuroblastoma cell line [Be(2)M17] to effectively block the transcriptional effects of TGOT (499).

B) BARUSIBAN. Barusiban (Ferring Pharmaceuticals) is a peptide, a potent and long-acting OXTR antagonist developed for preterm labor. It is a cyclic heptapeptide and an analog of endogenous OXT designed for longer duration of action (857). The binding domain of barusiban in the porcine OXTR is different from the natural agonist OXT, AVP, or the non-selective antagonist d$(CH_2)^5$[Tyr-$(Me)_2$,Thr^4, Orn^8,Tyr^9]-vasotocin (379, 834).

Although barusiban has been shown to inhibit OXT-induced contractions of human myometrial strips isolated from women who underwent cesarean delivery (825) and was effective in preventing OXT-induced preterm labor in cynomolgus monkeys (856), the clinical use of barusiban has been discontinued. A placebo-controlled, double-blinded study found that an intravenous bolus of barusiban was no more effective than placebo in stopping preterm labor in pregnant women at late gestation (1005).

C) EPELSIBAN. Epelsiban, also known as GSK557296, is an oral active non-peptide OXTR antagonist (K_i = 0.13 nM for the human OXTR) with >31,000-fold selectivity over the human V1a receptor and has been developed for the treatment of premature ejaculation in men (98, 931).

D) RETOSIBAN. Retosiban, also known as GSK-221,149-A is a promising oral active, potent and selective non-peptide OXTR antagonist with >1,400-fold selectivity over the related AVP receptors. Retosiban inhibited the procontractile effect of stretch on human myometrium (720) and was effective in preventing preterm labor in a placebo-controlled, double-blinded study in pregnant women (1006).

E) L-368,899. L-368,899 is a selective non-peptide antagonist of the OXTR, with >40-fold selectivity over AVP receptors (1091). This compound has a high oral bioavailability and crosses the blood-brain barrier with selective accumulation in areas of the limbic system (955). This accumulation was shown to block OXT-induced social and sexual behaviors (food sharing, sexual activity, parental behavior) (955).

F) L-371,257. L-371,257 is a selective non-peptide antagonist of the OXTR, with >800-fold selectivity over the AVP receptors (1092). It was one of the first oxytocin antagonists developed, and has good oral bioavailability, but poor penetration of the blood-brain barrier, which gives it good peripheral selectivity, with few central side effects (874). In adult male Sprague-Dawley rats, it had some facilitatory effects on vocalization (209). On a cellular level, L-371,257 has been shown to block the OXT-induced increase in neurite outgrowth, reduces neurite number (610, 611), and blocks the OXT-induced Ca^{2+} influx (1129).

F. OXTR Desensitization and Internalization

OXTR availability in the neuronal membrane is determined by *Oxtr* gene expression (see above), but also by desensitization and internalization of the receptor upon ligand binding. Desensitization of the OXTR upon agonist stimulation is a central phenomenon in how OXTR functioning is regulated (201, 877) and is initiated following ligand binding by phosphorylation of the OXTR via G protein-coupled receptor kinase 2. This kinase phosphorylates the receptor protein ~4 s after ligand binding (425) and primes it for subsequent β-arrestin2 binding. Recent studies revealed variants in OXTR phosphorylation sites among mammals, potentially leading to differential β-arrestin binding (1053). However, whether this diversity has any functional implications is not yet clear. In general, β-arrestin2 uncouples the OXTR from its G proteins and acts as a clathrin adapter (384) to allow the receptor being internalized in a clathrin pit-dependent mechanism (960). Dynamin, a large GTPase, is then able to pinch off the clathrin-coated vesicle (1065). Those vesicles are characterized by the expression of a specific type of protein, namely *Ras-related in brain 4/5* (201). These vesicles are stored intracellularly and are recycled back to the cell surface 4 h after internalization, as shown in transfected HEK293T and myometrial cells (201). Although binding of β-arrestin leads to internalization and uncoupling of the receptor from its G proteins, it is also essential for downstream signaling cascades, such as extracellular signal-regulated kinase (ERK1/2) or p38 (119, 401). It has been suggested that the use of functionally selective OXTR ligands, such as atosiban and DNalOVT, may be useful to study the isolated effects of OXTR activation with no accompanied β-arrestin binding (140, 974). Interestingly, OXTR internalization can also occur independent of β-arrestin, since it was shown using the selective OXT analog carbetocin (803). However, the functional components of this β-arrestin-independent internalization are unknown to date.

Prolonged or repeated receptor activation always implies a desensitized receptor and reduced membrane expression. This fact bears a risk for medication of human patients, since repeated daily intranasal application of OXT for several weeks or month could negatively interfere with peripheral or central membrane OXTR expression.

VI. OXTR-COUPLED SIGNALING IN BRAIN AND PERIPHERY

The quality of specific acute or long-term neuronal effects of OXT is dependent on the regional and subcellular presence of OXTR, the characteristics of OXT-OXTR binding, and subsequent activation of intraneuronal signaling cascades (1043, 1066). Duration and intensity of neuronal actions are mainly determined by the quantity of locally released OXT, OXTR affinity and density, local enzymatic cleavage, and, consequently, concentration of OXT in the surrounding extracellular fluid. In addition, the formation of OXTR homodimers or of heterodimers with other receptors are likely to influence OXTR affinity and downstream signaling.

The activation of OXTR homodimers by a homobivalent OXT analog, i.e., a ligand with a potential preference for dimers of the OXTR, separated by a well-defined spacer of 25 Å proved to be 100-fold more potent than OXT in activating G_q-protein signaling and 40-fold more potent in stimulating social behavior of heterozygous OXT knockout

mice in the three-chamber test. The bivalent analog binds to high-affinity state OXTR homodimers, whereas low-affinity state OXTR probably represents monomeric or oligomeric variants (138).

The OXTR also forms heterodimers with beta-2-adrenoreceptors, which leads to differential activation of downstream signaling cascades in myometrial and HEK293 cells (1104, 1105). Such receptor heterodimers activate a specific protein kinase C subform (protein kinase Cζ), causing attenuated downstream signaling compared with monomer-activated signaling. Additionally, OXTR were found to form heterodimers with dopamine D2 receptors in the dorsal striatum, with putative facilitating actions on social and emotional behavior (883). Evidence for heterodimers of the OXTR with the AVP receptors V1a and V1b has so far only been found in transfected HEK293 cells (998).

A. OXTR-Coupled G Proteins

In agreement with its major role in the promotion of uterine contractions during birth (361, 401, 1114), OXT-OXTR functions have mainly been studied in myometrial cells. The OXTR is characterized as a G protein-coupled receptor (GPCR); consequently, it is coupled to a trimeric complex of G proteins, consisting of one Gα and one β/γ unit. Upon ligand binding, the complex separates the β/γ subunit from the Gα-protein. Several different α-protein subforms can contribute to the composition of the complex. Depending on the type of Gα protein, the functional outcome of receptor activation can be stimulatory or inhibitory.

For instance, OXT stimulation of myometrial membranes resulted in coupling of the receptor to the activating $G\alpha_{q/11}$ and a decreased inward rectifying K^+ current, causing increased cell proliferation (567). In myometrial cells, the OXTR is coupled to the inhibitory G_α proteins (in detail: $G_{\alpha i1}$, $G_{\alpha i2}$, $G_{\alpha i3}$, $G_{\alpha oA}$ and $G_{\alpha oB}$) (140), which leads to reduced cell proliferation by OXT stimulation (392).

The state of G-protein coupling also depends on the physiological state of the animal. Cells from non-pregnant rat myometrium preferentially evoked OXT-induced Ca^{2+}-activated K^+ (BK_{Ca}) channel-mediated outward currents via the $G_{q/11}$/phospholipase C pathway leading to myometrial contractions. In contrast, in cells isolated from pregnant rat myometrium, OXTR activation increased the expression of $G_{\beta\gamma}$-stimulated adenylyl cyclase II, which suppresses Ca^{2+} transients and reduces myometrial contractility (1143).

In contrast to well-studied cell culture or membrane strip systems (138, 139, 469, 803, 862), first evidence for inhibitory coupling of a G_i protein to the activated OXTR in brain tissue has been found only recently in mice by applying the specific G_i-biased agonist atosiban (305).

B. OXTR-Mediated Calcium Currents

1. OXTR-induced Ca^{2+} release from intracellular stores

As described above, ligand binding to the OXTR results in the dissociation of the β/γ subunit from the trimeric G-protein complex that is coupled to the OXTR, thereby activating the Gα-protein. In addition to $G\alpha_q$-mediated phospholipase C activation (735, 865), the β/γ subunit also triggers the phosphorylation of the phospholipase Cβ3 (phospho-S^{1105}) (1141), and the OXT-induced generation of inositol-3-phosphate (IP_3) and diacylglycerol in primary and immortalized myometrial cells. There are three subtypes of IP_3 receptors, with subtle differences in their capacity to release Ca^{2+} from intracellular stores (900). At the same time, IP_3 receptors are governed by IP_3 and Ca^{2+} binding. This dual activation of IP_3 receptors is essential for the propagation of Ca^{2+} signals by Ca^{2+}-induced Ca^{2+} release from the endoplasmatic reticulum. Consequently, adjacent IP_3 receptors are activated, which in turn generates a spatial and temporal organization of IP_3-evoked Ca^{2+} release (842). The frequency of Ca^{2+} oscillations, but not spike amplitude or wave velocity, defines the strength of the GPCR-induced hormonal signal (60). Intracellular Ca^{2+} ions form complexes with the Ca^{2+} binding protein calmodulin. Ca^{2+}/calmodulin complexes activate the myosin light chain kinase, allowing myosin to cross-bridge to actin and cause smooth muscle contraction, for example, of myometrial cells during labor or of myoepithelial cells surrounding the milk ducts of the mammary gland. In addition to the IP_3-triggered intracellular Ca^{2+} release, in human myometrial PHM1 cells and primary myometrial cells, diacylglycerol is responsible for intracellular Ca^{2+} oscillations that depend on extracellular Ca^{2+} stores (932).

OXT not only affects peripheral cells but also induces the release of Ca^{2+} from intracellular stores in rat sensory neurons (44) and hypothalamic astrocytes (266). Primary astrocytes were isolated from 16-day-old embryonic rat hypothalami and cultured until treatment with 1 nM to 100 μM OXT. Ca^{2+} influx was dose-dependent and thapsigargin-sensitive, suggesting an involvement of IP_3 receptors, and removal of extracellular Ca^{2+} ions did not diminish the cellular response, suggesting no involvement of membrane Ca^{2+} channels (266).

2. OXTR-induced Ca^{2+} influx

Several Ca^{2+} channels have been shown to be involved in OXT-induced Ca^{2+} influx in human myometrial cells, i.e., canonical transient receptor potential (Trp) cation channels (TrpC) 1 (729), TrpC3 (932), TrpC4 (1037), and TrpC6 (188). Moreover, Ca^{2+} influx through voltage-operated Ca^{2+} channels (902) in addition to release from intracellular Ca^{2+} stores (903; see above) contribute to the full re-

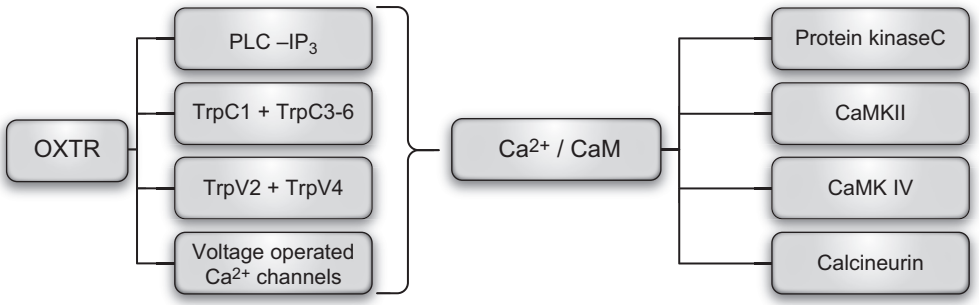


FIGURE 8. OXT-activated Ca2-channels and downstream signaling cascades. OXTR, oxytocin receptor; PLC, phospholipase C; IP3, inositol-3-phosphate; Trp, transient receptor potential channel; Ca^{2+}, calcium; CaM, calmodulin; CaMK, Ca^{2+}/calmodulin-dependent kinase.

sponse after myometrial OXTR activation. A negative feedback loop is provided by diacylglycerol-activated protein kinase C (PKC), which inhibits Ca^{2+} influx by TrpC3 and TrpC5 inhibition (1060). In addition, OXT triggers Ca^{2+} influx through Trp Ca^{2+} channels of the vanilloid type 4 (TrpV4) in myometrial cells regulated by the incorporation of the channel into the cellular membrane. This incorporation is prevented by β-arrestin 1 and 2 physically interacting with the TrpV4 channels. Thereby, TrpV4 is retained in the cytoplasm under basal conditions, whereas, during pregnancy, β-arrestin expression in the myometrium is reduced and membrane expression of TrpV4 increased to allow OXT-induced Ca^{2+} influx (1114) **(FIGURE 8)**.

OXT-induced Ca^{2+} influx also seems to play a role in neuronal OXT responses. We recently could show that OXTR activation leads to an incorporation of TrpV2 channels into the cellular membrane in a hypothalamic cell line. As found for TrpV4 in myometrial cells, incorporation of TrpV2 channels into the neuronal membrane is also a prerequisite for Ca^{2+} influx from the extracellular space (1044). This process is dependent on the activation of phosphoinositide-3-kinase (PI3K), since application of the PI3K inhibitor LY294002 prevented OXT-induced alterations in the amplitude and frequency of Ca^{2+} oscillations (1044). Moreover, in primary hypothalamic neurons, the OXT-induced increase in intracellular Ca^{2+} levels was prevented in Ca^{2+}-free medium confirming the extracellular source of Ca^{2+} (1044). The behavioral relevance of OXT-induced Ca^{2+} influx has been confirmed in adult male Wistar rats, since blockade of TrpV Ca^{2+} channels within the PVN prevented the well-established local anxiolytic effect of OXT specifically within the PVN (1044).

Blockade of the OXT-induced Ca^{2+}-influx by depletion of extracellular calcium in hypothalamic cells prevented downstream MEK1/2 phosphorylation (1044). Activation of the MAP kinase pathway within the PVN, specifically of MEK1/2 phosphorylation, was found to be one central factor for the anxiolytic effect of OXT in both males (89) and females (500). Consequently, Ca^{2+} influx is the prerequisite for the activation of further downstream second-messenger cascades and critical for OXT's behavioral effects.

3. Signaling cascades downstream of Ca^{2+} influx

Elevated intracellular Ca^{2+} levels from intracellular and extracellular sources described above were shown to be essential for some of the OXTR-coupled signaling pathways (see **FIGURE 9**). One Ca^{2+}-dependent pathway leads to

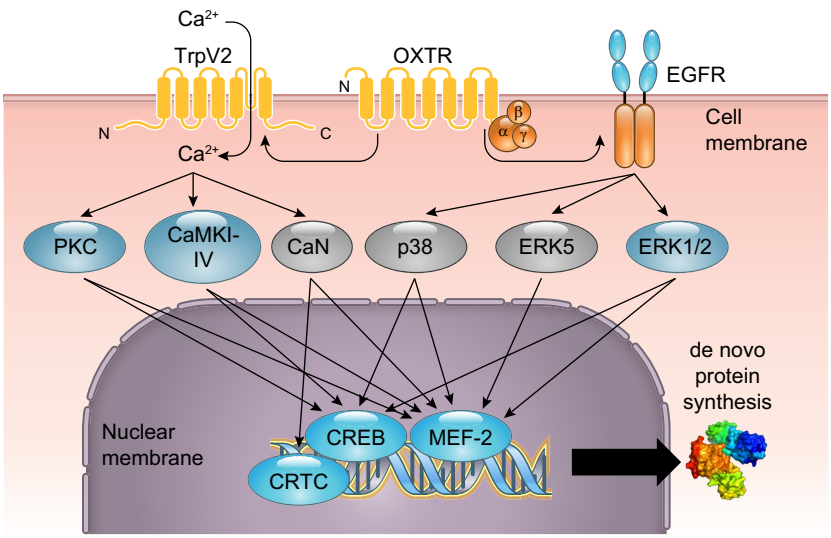


FIGURE 9. Representative scheme of neuronal OXTR-coupled signaling cascades. OXT binding to its receptor induces incorporation of TrpV2 channels into the cellular membrane and subsequent activation of Ca^{2+}-dependent cascades (PKC, CaMKI, II, IV, and CaN). OXT binding also induces transactivation of the EGFR and subsequent MAPK activation (ERK1/2, ERK5, p38). When direct evidence for coupling to OXTR in neurons is available, kinases are in blue circles. When indirect evidence is available or direct evidence from other cell types, kinases are in gray circles. All of the described cascades converge on the CREB-CRTC/MEF-2 transcription factor complex, leading to increased transcription of target genes. TrpV2, transient receptor potential vanilloid type 2; PKC, protein kinase C; CaMK, calcium/calmodulin-dependent kinase; CaN, calcineurin; EGFR, epidermal growth factor receptor; MAPK, mitogen activated protein kinase; ERK1/2, extracellular signal regulated kinase 1/2; CREB, cyclic AMP responsive element binding protein; CRTC, cyclic-AMP-regulated transcriptional co-activators; MEF-2, myocyte enhancer factor 2.

the dephosphorylation and activation of the eukaryotic elongation factor 2 (eEF2). eEF2 activation depends on protein kinase C (PKC), since blockade of PKC with the specific inhibitor Gö6983 inhibited its OXT-induced dephosphorylation. Activation of eEF2 by OXT leads to de novo translation of proteins as described in both myometrial cells (260) and neurons (Martinetz, Jurek, Meinung, von Schack, van den Burg, Slattery, and Neumann, unpublished observations). These newly synthesized proteins may exert trophic effects on myometrial cells, which would translate, under physiological conditions, into maintaining pregnancy. In neuronal cells, these newly synthesized proteins are potential mediators of long-term OXT effects.

In contrast to increased intracellular Ca^{2+} levels in OXT-stimulated neurons, OXT was reported to decrease Ca^{2+} levels in lipopolysaccharide-treated microglial BV-2 cells, thereby reducing pro-inflammatory factors (1125) and mitogenic signaling cascades (see sect. VIC). Interestingly, the expression of the glial OXTR is under the control of TGF-β of neuronal origin (703), thus differing from mechanisms controlling neuronal or myometrial OXTR expression. The differential effect of OXTR activation in glial cells and the distinct regulation of glial OXTR expression by TGF-β (released by neurons) indicates that the interplay between glial cells and neurons in OXT signaling is far from being understood and requires further in-depth investigation.

4. OXTR and calcineurin

Calcineurin is a Ca^{2+}-activated phosphatase that is ubiquitously expressed in brain and periphery. Numerous studies revealed a coupling of the OXTR and calcineurin, for instance, OXT-induced contractions of smooth muscle cells in the myometrium are dependent on activation of calcineurin (830). In the brain, calcineurin is known to be involved in the regulation of memory formation in the hippocampus (572, 697) and in the regulation of anxiety and fear conditioning in the amygdala (64, 620), a region known to be modulated by OXT (1067). The underlying molecular mechanism of fear and anxiety regulation also involves calcineurin-induced diminished CRF receptor 1-mediated signaling (451).

Calcineurin also affects the phosphorylation status of a transcriptional cofactor of CREB, named CREB-regulated transcription coactivator (CRTC1), also named TORC1 (561), and CRTC2 (TORC2) (923), thereby dissociating CRTCs from the scaffolding protein 14-3-3. Subsequently, free CRTCs are able to translocate to the nucleus. The factors CRTC, p300, MEF-2, CREB, and others form a transcriptional complex to induce stimulus-dependent gene transcription (485, 499, 625, 626).

To date, the only direct evidence for a coupling of the OXTR to calcineurin in humans stems from cultured human myometrial cells (830, 1108).

C. OXTR and MAP Kinase Pathways

1. OXTR link to the epidermal growth factor receptor and the MAPK pathway

Not only intracellular Ca^{2+} but also multiple other pathways are linked to the OXTR leading, upon stimulation, to the activation of mitogen-activated protein kinase (MAPK) via activated receptor tyrosine kinases, such as the epidermal growth factor receptor (EGFR) (89). This receptor has been associated with MAPK activation due to its tyrosine kinase activity. The involvement of EGFR in OXTR-MAPK signaling has been proven by blocking OXT-induced MAPK phosphorylation by the non-selective EGFR inhibitor tyrphostin AG1478 in hypothalamic 4B cells (89), rat hippocampal slices (621), and rat and bovine myometrial cells (563, 1142). However, the nature of the signal carrier that links the OXTR to the EGFR is unknown to date. After OXT-induced activation, the EGFR recruits the membrane-associated proto-oncoprotein GTPase Rat sarcoma (Ras) as the initiator of the MAPK pathway. In a subsequent chain of events, Ras phosphorylates its downstream MAP kinase kinase kinase (Map3k) c-Raf-1 (337) as fast as 5 min after the onset of OXT stimulation in a rat hypothalamic cell line (89), leading to full activity of MAPK pathway.

2. OXTR and MEK1/2-ERK1/2

The MAP kinase kinase 1 and 2 (MEK1/2) is one of the best-studied proteins of the MAP kinase pathways. There are three main subfamilies of MEK proteins: MEK1/2 (Map2k1/2), MKK3/6 (Map2k3, SKK2/Map2k6, SKK3), and MKK4/7 (Map2k4, SEK1/Map2k7, SKK4); those three subfamilies are the main kinases for the central proteins of the MAPK pathways: ERK1/2, p38, and c-Jun NH_2-terminal kinase (JNK1/2/3) (575). The coupling of the OXTR to these main MAPK pathways has been intensively investigated in nonneuronal and neuronal tissue and cell lines (499, 500, 528, 621, 999, 1103).

MEK1/2 and Raf-1 have both been found to be activated by OXT in small cell lung cancer cells (812), myometrial cells (1103), and primary amnion cells (528). MEK1/2 is also phosphorylated in OXTR-expressing macrophages during inflammation (988). In the brain, MEK1/2 and its active phospho-form is found in OXT-positive neurons of the PVN and SON during late pregnancy or after OXT infusions in male and female rats (89, 171, 499, 500, 1044) and in dorsal hippocampus, but not in medial prefrontal cortex neurons that were activated by a local infusion of OXT (416). Downstream of MEK1/2, in addition to the well-studied ERK1/2, alternative MEK1/2 targets have been identified, such as PPARγ, MyoD, PI3K, or LIMKinase 1 in a variety of tissues (111, 133, 490, 543). These findings imply the possibility of MEK1/2 signaling independent of ERK1/2 phosphorylation.

However, the canonical target of MEK1/2 is ERK1/2, and its OXT-induced activity has been detected in peripheral tissues, such as cardiomyocytes, where it prevents hypertrophy (691), osteoblasts, where it induces maturation (264), or human mesenchymal stem cells, where it reverses osteoporosis (303). OXT-induced contraction of myometrial cells was found to be ERK1/2-dependent in both rat and human cells (767, 1749). In addition, OXT leads to prostaglandin E2 expression in an ERK1/2-dependent manner in human amnion cells (999). Surprisingly, ERK1/2 phosphorylation was detected only after 6 h of OXT stimulation (999). This late onset of MAPK activity is surprising when compared with hypothalamic tissue where ERK1/2 activity is being detected already after 10–30 min (89, 499, 500, 1044, 1078).

In contrast to those findings, ERK1/2-independent OXTR signaling was detected in a variety of prostate cancer cell lines (1140). Cellular migration in prostate cancer cells is known to be EGFR- and ERK1/2-dependent; however, Zhong and colleagues (1140) observed OXT-induced cellular migration independent of EGF or ERK1/2, highlighting again the tissue- and cell-type specific coupling of signaling cascades to the OXTR. Moreover, in CHO cells transfected with the rat OXTR, OXT induced ERK2, but not ERK1 phosphorylation, leading to prostaglandin E2 synthesis (975) via the rate limiting enzyme COX2 (1103).

Indeed, our own data support this scenario of differential ERK1/2 activation. In the PVN of lactating rats (*lactation day 8*), MEK1/2 phosphorylation is upregulated, with concomitant nuclear translocation of ERK1, but not ERK2 (500). When exogenous OXT was applied icv to lactating females, MEK1/2 phosphorylation in the PVN was even reduced, with no subsequent changes in ERK1/2 activity (500). Interestingly, phosphorylation-independent functions of ERK1/2 have been described in a variety of cellular and genomic processes (880), so that a role for non-phospho ERK1/2 during lactation cannot be excluded. In addition, stimulation of brain slices containing the SON with 10 pM OXT led to an increase of cytosolic phosphorylated ERK1/2 in neurons with no nuclear translocation, indicating cytosolic targets of ERK1/2 that render nuclear translocation unnecessary (1078).

Taken together, mounting evidence suggests a cell-type and tissue-specific differential activation of the OXT-induced MEK1/2-ERK1/2 pathway in neurons and peripheral cells, with *1*) full ERK1/2 activation, *2*) differential ERK1 or ERK2 activation, *3*) ERK1/2 phosphorylation peaks ranging from 10 min to 6 h, and *4*) pERK1/2-independent signaling downstream of active MEK1/2.

3. OXTR and PEA-15

The "phospho-protein enriched in astrocytes 15 kDa" (PEA-15; also PED = phospho-protein enriched in diabetes) is abundantly expressed in brain, heart, and adipose tissue. PEA-15 acts as inhibitor of the MAPK pathway by binding and retaining ERK2 in the cytoplasm. This activity of PEA-15 is intriguing, considering the findings of Wang and Hatton, who found OXT-induced phosphorylated ERK2 to be retained in the cytoplasm (1078). Moreover, dysregulation of the ERK pathway in PEA-15 knockout mice leads to impaired spatial learning and heightened stress reactivity and/or anxiety in limited instances (853). In more detail, PEA-15 activity is regulated by a hierarchical control executed by CaMKII phosphorylating PEA-15 Ser116, which in turn enhances the ability of another upstream kinase, PKC, to phosphorylate PEA-15 at Ser104 (568). Both CaMKII and PKC are activated by the OXTR (260, 499), and our own unpublished data show an increased phosphorylation of PEA-15 at both phospho-sites after 30 min of OXT stimulation in hypothalamic H32 cells. Although the role of OXT in diabetes is somehow controversial (16; sect. X), the role of PEA-15 in regulating ERK activity is one potential factor to be considered for treatment of diabetes and obesity with OXT.

Moreover, PKB/Akt (see below) seems to phosphorylate PEA-15 and stabilize its anti-apoptotic actions in HEK293 cells, thereby providing one molecular mechanism for the pro-survival/viability effect of OXT on a variety of cell types (1026; see sect. VII).

4. OXTR, protein kinase B (Akt), and phosphatase and tensin homolog (PTEN)

Protein kinase B (or Akt) has been found to be involved in OXTR-coupled signaling pathways in several tissues, including endothelial cells of the umbilical vein (165), villus-crypt enterocytes of the gut (542), cardiomyocytes (409), and endometrial cancer cells (254). Activation of protein kinase B by OXT leads to cellular migration, regulation of translation, and regulation of gut development (542). The activity of Akt is regulated by Ser473 and Thr308 phosphorylation by phosphoinositide-dependent kinase 1 (PDK1). A counteracting enzyme is the phosphatase and tensin homolog (PTEN). Germline mutations in PTEN are associated with macrocephaly and autism spectrum disorder, whereas conditional deletion of PTEN in oxytocinergic neurons affect cell structure but not autism-relevant behaviors in mice (193). Whether those mutations disrupt OXT-induced signaling via protein kinase B is currently unknown.

5. OXTR signaling does not alter JNK activity

The JNK1/2/3 are members of the MAPK family, but, unlike MEK-ERK, their activity is often associated with many forms of stress, including cellular inflammatory stress (346), apoptosis and necrosis (731), or physical stress during the forced swim paradigm in the rat hippocampus, hy-

pothalamus, and amygdala (629). In murine microglia cells that have been treated with lipopolysaccharide (LPS) to mimic inflammation, ERK1/2, p38 (see below), and JNK1/2/3 are phosphorylated. Treatment of those cells with OXT leads to a decrease of LPS-induced ERK1/2 and p38 but not JNK phosphorylation (1125). This data is in line with our unpublished observations that OXTR activation in hypothalamic neurons does not alter JNK1/2/3 phosphorylation.

6. OXTR and p38

The MAPK p38, also known as MAPK14, plays a role in a variety of processes, ranging from regulation of CRF gene expression in the hypothalamus (503) to synthesis of inflammatory cytokines (530, 888) in human myometrium and amnion. p38 has been shown to be activated by OXT in myometrial cells (119, 260, 530) and heart tissue (786). However, the downstream targets of OXT-induced p38 have not been further explored and remain to be elucidated.

7. Scaffolding protein 14-3-3

Interactions between proteins are based on scaffolding proteins that bring second-messenger kinases in close proximity. Scaffolding proteins such as 14-3-3ζ (also known as Ywhaz) are either inhibitors or activators of MAPK signaling, depending on their phosphorylation status. The status of phosphorylation and even transcription levels of Ywhaz are regulated by several factors, e.g., water deprivation and osmotic stress, which was found to affect OXT and AVP neurons of the SON (390). The regulation of *Ywhaz* gene expression in OXTergic neurons by environmental stimuli renders this gene an inappropriate housekeeping gene (as suggested by Ref. 95) for OXT- or stressor-related studies of gene transcription by means of qPCR and should be considered carefully.

8. OXTR and β-arrestin

In general, binding of OXT to its receptor leads to phosphorylation of the OXTR by a special GPCR kinase, which allows the recruitment of β-arrestin. B-arrestin recruitment leads to desensitization and internalization of the OXTR (137, 402), but is also essential for correct induction of MAPK signaling (401; see sect. V*F*). However, OXTR internalization can also appear to be β-arrestin-independent, for instance when induced by the OXT analog carbetocin (803). In addition, β-arrestin can also directly bind and sequester TrpV channels in the cytoplasm, as seen in myometrial cells, thereby inhibiting OXT-induced Ca^{2+}-signaling (see sect. VI*B*). This effect has been detected in the non-pregnant mouse uterus but is absent in pregnant uteri (1114). In murine osteoblasts, β-arrestins facilitate the translocation of the OXTR to the nucleus, a process never described before in other cell types (264).

9. OXTR and ERK5

The OXTR has also been linked to activation of the related big MAP kinase, ERK5 (also known as BMK1 or MAPK7), as shown in myometrial cells (261). In general, ERK5 promotes expression of the myosin light chain gene and has a central role in the development and differentiation of a variety of cells (382) but also promotes cell death (1139). Although direct evidence is missing, ERK5 is also likely to be coupled to the OXTR in neuronal cells, since one upstream regulator of ERK5 is PKCζ, a kinase directly coupled to OXTR-β2-adrenergic receptor heterodimers found in neurons (1104). In addition, in a variety of cell lines (CHO, HEK293, Cos7, and HeLa), PKCζ serves as scaffolding protein between Gαq-proteins and ERK5, leading to direct activation of ERK5 by Gαq without involvement of the canonical upstream kinases MEK5 or phospho-lipase C (905). Evidence for neuronal OXTR-coupling to ERK5 was also provided by the finding that ERK5 might be involved in the OXTR-mediated regulation of anxiety-related behavior in rats. In support of data showing a direct link of the OXTR to ERK5 (261), application of the MAPK inhibitor UO126, which blocks both MEK1/2 and ERK5 activity (261, 706), abolished the local anxiolytic effect of OXT within the PVN (89). However, whether MEK1/2, ERK5, or both pathways in conjunction mediate this behavioral effect is currently not known.

Downstream target of OXT-induced ERK5 is most likely the family of MEF-2 transcription factors (described in more detail in sect. VIC11; see Refs. 261, 467), exerting effects on apoptosis, cellular viability, synaptic plasticity, and dendritic outgrowth (467, 835).

10. OXTR and the transcription factor MEF-2

The myocyte enhancer factor 2 (MEF-2) is a transcriptional regulator that might act as effector of some of the OXTR-coupled signaling cascades described above **(TABLE 5)**. We summarize here the evidence for a link between MEF-2 and the OXTR, which might help to understand the molecular mechanism underlying the behavioral effects of OXT.

MEF-2 is a transcription factor family consisting of four subtypes (MEF-2A, B, C, D), whose expression pattern partly overlaps with those of the OXTR, since it was found in neurons, smooth muscle cells, bone, lymphocytes, and endothelial cells (84, 302, 927). All MEF-2 subforms share a common genetic structure: the DNA binding domain, the MEF2 domain (provides better sequence binding specificity), and a COOH-terminal transcriptional regulatory domain, whose activity is orchestrated by multiple posttranslational modifications (1131). MEF-2 is implicated in dendritic remodeling, neuronal differentiation and proliferation, growth, and apoptosis. Dysfunctional MEF-2 has been associated with autism (724), amyotrophic lateral sclerosis (37), mental retardation, Alzheimer's, and Parkinson disease (344, 835).

Table 5. *Selection of proteins involved in OXTR-coupled signaling cascades, their function, time frame of activity, potential behavioral or functional context, and related publication*

Protein	Protein class	Timing	Tissue	Phenotype/Function	Related Publication
Ras	Kinase	3–5 min	Rat hypothalamic H32 cells	Anxiety	89
Raf	Kinase	5 min	Rat hypothalamic H32 cells	Anxiety	89
MEK1/2	Kinase	5–30 min	Rat hypothalamic H32 cells, mouse hippocampal slices, rat hypothalamic tissue, human myometrial and amnion cells	Anxiety, spatial memory, inflammation	89, 514, 515, 544, 1042, 1075
ERK1/2	Kinase	10 min to 1 h	*Tissue*: human and rat myometrial cells, rat hypothalamic (PVN) tissue, rabbit and human amnion cells, rat hippocampal synaptoneurosome *Cell lines*: ULTR, CHO, HEK-293, bEEL, NCL-H345, NCL-H146, H32, hTERT-C3, MDCK *Primary cells*: human primary macrophages, THP-1, and murine macrophages	Anxiety, spatial memory, smooth muscle contraction, PGE2 and PGF2 synthesis, inflammation, cell proliferation, differentiation, long term potentiation, anti-hypertrophic	89, 120, 261, 263, 266, 305, 411, 501, 514, 515, 579, 641, 713, 793, 837, 889, 899, 955, 1004, 1017, 1021, 1029, 1042, 1109, 1134, 1135
Ribosomal protein S6 kinase B1	Kinase	20–30 min	Caco2BB cells	?	558
RSK1/2	Kinase	?	Murine and human prostate cells, rat hypothalamic PVN	?	1140; unpublished observations
MSK 1/2	Kinase	?	Rat hypothalamic PVN	?	Unpublished observations
MEK5	Kinase	?	Myometrium	?	262
ERK5	Kinase	30 min	Myometrium	?	262
p38α	Kinase	?	Human and rabbit amnion cells, human myometrial, hTERT-C3 cells, rat ventricular heart tissue, ULTR cells, CHO, mouse embryonic stem cells, mouse osteoclast cells	Protein synthesis, bone formation, cardioprotection	120, 261, 459, 501, 544, 811, 1021, 1159
JNK1/2/3	Kinase	–	Hypothalamic H32 cells		Unpublished observations
PEA-15	scaffolding protein	10–90 min	Hypothalamic H32 cells	Regulation of ERK signaling	Unpublished observations
PTK2B	Kinase	1 h	Human umbilical vein endothelial cells	Angiogenesis	167
CaMKI	Kinase	5–10 min	Hypothalamic H32 cells	?	Unpublished observations
CaMKII	Kinase	5–10 min	Hypothalamic H32 cells	?	514, 1075

Continued

Table 5.—*Continued*

Protein	Protein class	Timing	Tissue	Phenotype/Function	Related Publication
CaMKIV	Kinase	5–10 min	Hypothalamic H32 cells	?	Unpublished observations
Caldesmon	Calmodulin binding protein	15 min	Human myometrial cells	Contraction	955
PKA	Kinase		Hypothalamic H32 cells, mouse embryonic stem cells	Expression of connexin43	1159; unpublished observations
PKB (Akt)	Kinase	30 min	Mouse osteoclasts, rat ventricular heart, hippocampal synaptoneurosomes, MCF7, HT29, Caco2BB cells, rat H9c2, rat neonatal cardiomyocytes, human umbilical vein endothelial cells	Long-term potentiation, angiogenesis, cardioprotection	167, 392, 558, 559, 641, 713, 811, 853, 1021
PKC	Kinase	5 min	Myometrium	Smooth muscle contraction	261
β-Arrestin	Scaffolding protein	5–10 min	Myometrium, HEK cells	Receptor desensitization	411
EGFR	Receptor	5 min	Rat hypothalamic H32 cells, rat synaptoneurosomes, MDCK and HEK293 cells, COSM6 cells	Anxiety	89, 641, 899, 1174
PLC	Lipase	3 min	Human myometrial cells	Smooth muscle contraction	386, 1173
AMPK α1	Kinase		Mouse cardiomyocytes	Energy sensor	853
Pi3K	Kinase	?	Hypothalamic cell culture	Anxiety	1075
mTOR	Kinase		Hypothalamic H32 cells, rat hypothalamic tissue (PVN), Caco2BB cells	Central signaling kinase	558; unpublished observations
c-Jun	Transcription factor		Hypothalamic H32 cells		Unpublished observations
elk-1	Transcription factor		Hypothalamic H32 cells		Unpublished observations
MEF-2A	Transcription factor	?	Rat hypothalamic tissue (PVN)	Synaptic plasticity	Unpublished observations
MEF-2B	Transcription factor		Rat hypothalamic tissue (PVN)	Synaptic plasticity	Unpublished observations
MEF-2C	Transcription factor	?	Rat hypothalamic tissue (PVN), myometrial cells	Synaptic plasticity, autism	262, 349
MEF-2D	Transcription factor	?	Rat hypothalamic tissue (PVN)	Synaptic plasticity	Unpublished observations
CREB	Transcription factor	20 min to 1 h	Hypothalamic H32 cells, rat hypothalamic tissue (PVN), mouse hippocampal slices	Anxiety, stress, spatial memory	514, 1042
eEF2	Translation elongation factor	5–60 min	hTERT-C3 cells, rat epididymal adipose tissue	Anxiety	261, 301

Continued

Table 5.—*Continued*

Protein	Protein class	Timing	Tissue	Phenotype/Function	Related Publication
CRTC2	Transcriptional cofactor		Hypothalamic H32 cells, rat hypothalamic tissue (PVN)	Stress	514
CRTC3	Transcriptional cofactor	10 min to 1 h	Hypothalamic H32 cells, rat hypothalamic tissue (PVN)	Stress	514
RGS2	Regulator of signaling cascades	1–2 h	Amygdala in vivo	Anxiety	806
NF-κB p65	Transcription factor	15–30 min	Human myometrial and amnion cells, mouse embryonic stem cells,	Inflammation	472, 544, 1159
IKK1 (CHUK)	Inhibitor of NF-κB	15–30 min	Human myometrial and amnion cells	Inflammation	544
IKK2	Inhibitor of NF-κB	15–30 min	Human myometrial and amnion cells	Inflammation	544
Connexin43	GAP junction channel	3 h	Mouse embryonic stem cells	Intercellular communication	1159
PTEN	Phosphatase	30 min	Caco2BB cells		559
cd38	Cluster of differentiation	5 min	Mouse hypothalamus	Social behavior	654

–, No link to OXT; ?, unknown.

There is a bifunctional regulation of gene transcription by MEF-2 proteins. This regulation is an inherent property that arises through different phosphorylation sites in the MEF-2A–D proteins. For instance, phosphorylation of MEF-2A at Ser387, Thr312, and Thr319 by p38 is known to stimulate gene transcription (415), whereas phosphorylation at Ser408 by cyclin-dependent kinase 5 turns MEF-2A into a transcriptional repressor (383). Following activation of (OXTR-coupled) signaling cascades, such as CaMKII, MEK1/2, cdk5 (82), ERK5 (467), SIK, calcineurin, and p38 (261, 343, 637, 1103, 1138), MEF-2 is phosphorylated, homo- or heterodimerizes, and is released from class II histone deacetylases (HDACs), which suppress MEF-2 activity under basal conditions (268). Each member of the class II HDACs is expressed in oxytocinergic neurons of the PVN (989), and each of the upstream kinase pathways is coupled to the OXTR (260, 499, 528), suggesting close interactions between the OXT system and the MEF-2 pathway. Indeed, activation of MEF-2 by the OXTR via ERK5 has already been shown in myometrial cells (261).

Taken together, these data strongly implicate a role of OXT-induced MEF-2 activity in the regulation of anxiety. As a transcription factor, MEF-2 was shown to regulate stress- and anxiety-related target genes, such as *Rgs2* or *Pacap* (345), which also have been implicated in the anxiolytic effect of OXT (781, 801).

11. OXTR, the transcription factor CREB and its cofactor CRTC (TORC)

Signaling cascades, like the above mentioned, converge on a set of transcription factors to exert their target-specific effects. In brain areas, such as the hippocampus, the OXTR-EGFR-MEK1/2 cascade has already been shown to trigger phospho-CREB-dependent spatial memory formation during motherhood (1011) and long-term potentiation (621). In support, peripheral administration of OXT either acutely or repeatedly (1 mg/kg OXT daily for 2 wk) promoted hippocampal cell proliferation, adult neurogenesis, and dendritic maturation (906). Blockade of the MAPK pathway by U0126 blocked the proliferative effects of an acute ip OXT treatment in the hippocampus (612). It is, therefore, tempting to speculate that some of the OXT-CREB-regulated genes that are important for spatial memory formation are associated with synaptic plasticity, such as brain-derived neurotrophic factor (*Bdnf*). Indeed, a link between OXT treatment and *Bdnf* expression has been found in the hippocampus of neonatal and adult rats (49, 431) and mice (255). Interestingly, activation of CREB alone is not sufficient for inducing *Bdnf* transcription. Instead, the transcriptional regulation of *Bdnf* is also dependent on CRTC (TORC) (336). We have recently found a link between OXT and CRTC by demonstrating that OXTR activation delays stress-induced translocation of CRTC3 to the nu-

cleus, thereby altering the transcription of CRTC-dependent genes (499). Surprisingly, OXT had a specific impact on CREB/CRTC3-regulated gene transcription, since the nuclear translocation of the closely related CRTC2 was not affected by OXTR activation.

The intracellular signaling pathway that couples the OXTR to CRTC3 is currently not known. One protein kinase known to regulate CRTC phosphorylation and nuclear trafficking is the salt-inducible kinase (SIK) (190, 909). SIK is a member of the mammalian AMP-activated protein kinase (AMPK) family. AMPK was found to be activated by OXT in skeletal muscle cells (347, 599). Thus it is possible that the OXTR also activates SIK, e.g., by increasing intracellular Ca^{2+} levels.

D. The Problem of Signal-Target Specificity: Factors to Consider About OXTR Signaling Cascades

We have to consider, how a single nonapeptide (OXT) released into different body compartments in different physiological and psychological contexts (stress, lactation, social contact, exercise…) is capable of creating target- and tissue-specific responses on a cellular or behavioral level via binding to and activation of one single receptor type: the OXTR. On a cellular level, the OXTR activates numerous Ca^{2+}-related and MAPK-related signaling cascades in a variety of cell types. However, this seemingly random and redundant activation pattern becomes meaningful when several factors are taken into account:

1) The OXTR can assume two different affinity states, high vs. low, depending on the presence of cholesterol and Mg^{2+} ions in the membrane. Heterodimerization with other receptors (βAR, 5HT receptor, and AVP receptor), $G_{\alpha q}$ or $G_{\alpha i}$ coupling to the receptor, internalization, and β-arrestin recruitment also differentially affect downstream signaling cascades, allowing the receptor to induce a specific cellular response to OXT binding in a specific context.
2) Ca^{2+}-related pathways typically act faster than MAPK pathways, thereby creating a temporal pattern of signaling cascade activity that drives a cellular response from 1 to 5 min (Ca^{2+}-related) up to 4 h (MAPK-related). A typical example is the phosphorylation pattern of CREB. Although CaMKIV mediates the early phase of CREB phosphorylation, the MAPK pathway is responsible for prolonging it (1106).
3) A defined subset of cascades work in conjunction to activate a specific set of transcription factors and cofactors (e.g., CREB and CRTC), which in turn can only regulate genes that depend on the binding of both, the factor and its cofactor. If one of them is missing, those target genes remain silent (e.g., CRF; see Ref. 499).
4) Signaling cascades coupled to the OXTR in neurons are not necessarily present in peripheral smooth muscle cells of the myometrium, blood cells, or other organs further providing cell-specific responses to OXT.

VII. OXTR-MEDIATED CELLULAR EFFECTS

The signaling cascades described above are the intracellular messengers that carry an extracellular signal to its cytoplasmic or nuclear target to orchestrate the cellular response to the stimulus. This response defines the later outcome on a circuit level, which will ultimately result in a phenotypical or behavioral adaptation of the whole organism. However, it is still largely unknown, how OXT regulates cellular, especially neuronal, functions.

Glutamatergic hippocampal neurons expressing the OXTR are an adequate cellular model that can be studied in primary in vitro cultures or hippocampal brain slices. For instance, transient stimulation of primary neuronal cultures with OXT for 3 days decreased dendritic branching in an OXTR-dependent manner, assessed by Scholl analysis (876), but exclusively in glutamatergic neurons identified via VGLUT1 expression. This effect was found to be $G\alpha_{q/11}$-dependent, since blockade with the PLCβ inhibitor blocked the OXT-induced morphological alterations. In addition, the overlap between VGLUT1, indicative of the presynaptic compartment, and PSD-95, indicative of the postsynaptic compartment, decreased with OXT treatment, suggesting a decrease in the number of excitatory synapses by OXT (876). In line, OXT treatment (100 nM) directly decreased synaptic transmission in glutamatergic neurons, assessed as a reduced amplitude of evoked excitatory postsynaptic currents (EPSCs) (876).

Somewhat contradicting data from human neuroblastoma (SH-SY5Y) cells showed a stimulatory effect of OXT (1 μM) on neurite outgrowth (610). This increase was accompanied by increased expression of dendritic marker proteins, such as nestin, vimentin, cofilin, and drebrin. The contradicting reports on the actions of OXT on neurite outgrowth might be explained by the gender and species of the donor (neuroblastoma cells isolated from a 4-yr-old girl (SH-SY5Y) vs. primary neurons from non-gender-specified mouse embryos, different OXT concentrations (100 nM vs. 1 μM), or simply by a cell type-specific effect.

In the same SH-SY5Y cells, OXT exerted a positive effect on cell viability and cell growth, assessed by an MTT-(3-(4,5-dimethyl-thiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, and cell number counting (50). Despite the high OXT dose applied, the cell number counts were dose-dependent, with the highest number of cells de-

tected at 1 μM OXT for 96 h. This positive effect on cell proliferation was also found in the related neuroblastoma cell line SK-N-SH and the glioblastoma cell line U-87 MG (50). In addition, OXT facilitated the prolongation of neurites in the astrocyte-like cell line U-87 MG (611), although previous studies found OXT-induced retraction of glial coverage of hypothalamic neurons, consequently leading to increased excitability in those regions (1003).

VIII. OXTR-MEDIATED REGULATION OF BEHAVIOR IN ANIMALS AND HUMANS

Social, stress-related, and anxiety-related behaviors have been evolutionarily manifested as critical factors for the survival and biological success of mammals. The development of complex social interactions and multiple forms of attachment between sexual partners, individuals of a family or a group, but also between members of different groups, appear to be a driving force for the development of complex brain structures and the enlargement of the brain (295). All kinds of social attachment provide a feeling of safety, reduce predator risk, anxiety and stress levels, and thus promote general fitness and reproduction. The various members of the OXT and vasopressin families are strongly involved in the regulation of stress- and anxiety-related responses, and in the regulation of these highly species-specific social behaviors. Their roles in facilitating social behaviors have been as evolutionary conserved as the molecular structure of the nonapeptides, their receptors, as well as the neuronal expression patterns within the brain (280, 398, 746). Here, we limit the discussion about the behavioral relevance of OXT to mammals including humans.

The effects on learning and memory functions (247), on sexual behavior (687), and the promotion of maternal behavior (809) in rodents were the first reported behavioral effects of the two closely related neuropeptides OXT and AVP in the 1960s and 1970s. Interestingly, in the 1980s and 1990s, the AVP system dominated scientific interest due to its anxiogenic and depressive-like effects and, thus, for the potential to target the brain AVP system in psychopathologies associated with increased anxiety level or depression-related symptoms (for review, see Refs. 351, 753). However, research in this direction has come almost completely to an end due to a lack of clinically efficient selective AVP antagonists (755). In contrast, the discovery of anxiolytic, anti-stress, and complex pro-social effects of OXT in various mammals has promoted the scientific focus on this nonapeptide since the 1990s. This trend has been further facilitated by the discovery of a plethora of OXT effects on human behaviors after its intranasal (i.n.) application. In general, there is strong agreement that OXT promotes multiple aspects of socio-emotional and socio-sexual behaviors, improves learning and memory abilities, modulates feeding, grooming, and drug-seeking behavior, as well as the activity of stress and pain systems, which will be discussed in detail below.

Behavioral effects of brain OXT come about after its release from axon/collateral terminals within forebrain or other limbic target regions, or from somata and dendrites within the hypothalamic PVN and subsequent binding to its receptors, as described above. Here, we will discuss studies, which revealed the role of the *endogenous* OXT system in behavioral regulation by pharmacological or pharmacogenetic manipulation of local OXT or OXTR expression, of intracerebral OXT release or of OXT-OXTR interactions. We will also discuss animal behavioral studies, which infused *synthetic* OXT or an OXTR antagonist either icv or directly into a brain target region expressing the OXTR. Some studies used peripheral injections of synthetic OXT, although detailed mechanisms of nonapeptide uptake across the blood-brain barrier are unknown **(FIGURE 10)**. Most of these studies were performed in laboratory rats and mice, but also studies on sheep, voles, or non-human primates contributed significantly to our growing knowledge on the behavioral effects of OXT.

Finally, we will also discuss selected human studies using the i.n. route of OXT administration in the context of behavioral and neuronal (fMRI) effects of OXT. Since the appearance of the first human study using i.n. OXT in the context of behavioral and neuronal effects in 2003 (432) and 2005 (537, 554), the number of published human studies on i.n. OXT has been steadily growing to 18 in 2010, 83 in 2014, and 96 in 2016.

A. Regulation of Male and Female Sexual Behavior

Sexual behaviors represent one of the most important strategies to guarantee the survival of a given species, thus being highly conserved throughout evolution. The repertoire of sexual behaviors displayed by all mammals is rather similar, of course with varying and species-dependent differences in the temporal sequences of specific behavioral patterns. OXT is one of the neuropeptides and factors, which is essential for many aspects of these stereotyped sexual behaviors in both males and females.

1. Male sexual behavior

The most detailed research, by far, concerning the neurobiology and neuroendocrinology of sexual behavior has been performed in rodents, predominantly in rats. Sexual behavior in male and female rodents is divided into pre-copulatory and copulatory behaviors (821, 1057). In the appetitive, pre-copulatory phase of the sexual sequence, the male displays chasing and sniffing of the sexually receptive fe-

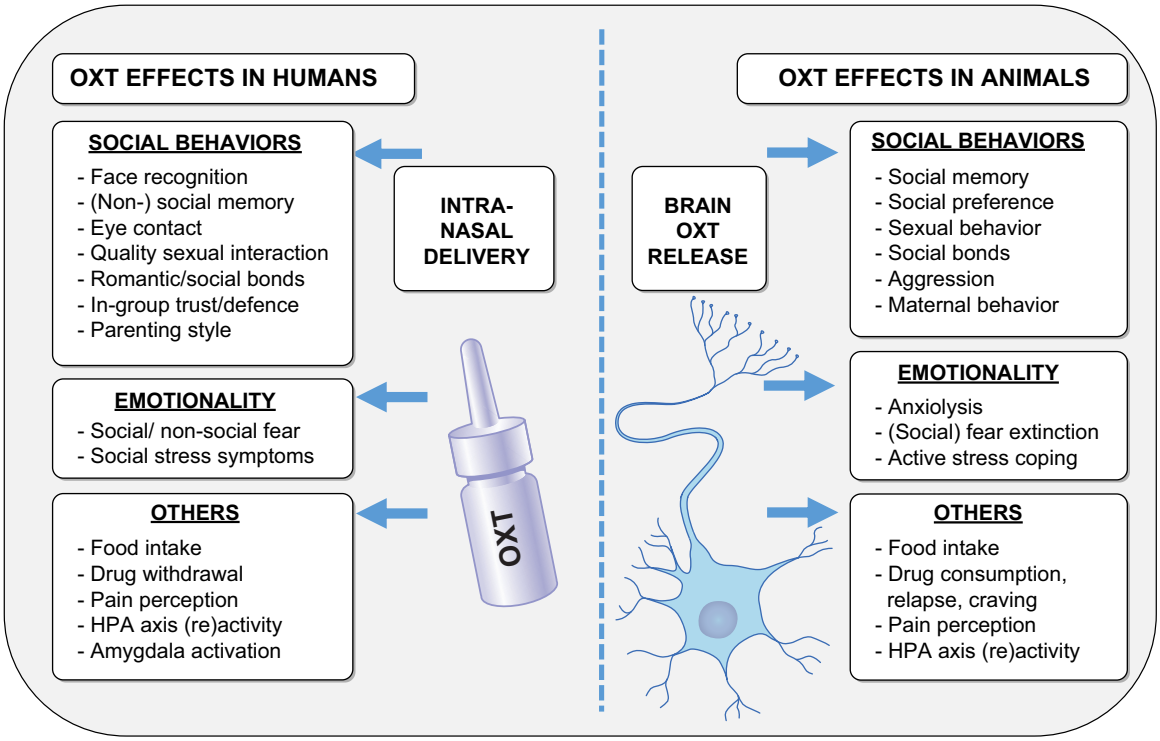


FIGURE 10. Summary of effects of synthetic or endogenous OXT on social behaviors, emotionality, and other functions reported in humans after intranasal delivery (*left*) and in animals (*right*).

male, which results in sexual arousal. The pre-copulatory phase is also characterized by the phenomenon of "desire" (380, 820, 1057). OXT significantly contributes to sexual arousal and expectancy of future reward (97), especially via interactions with the dopamine system to increase sexual desire.

Male copulatory behavior is composed of mounting, intromission, and ejaculation, with profound evidence for an involvement of OXT. Sexual cues and the performance of sexual behavior strongly activate the OXT system, as indicated by increased Fos-expression in a specific subset of parvo- and magnocellular OXT neurons of the PVN and SON of male rats (155, 766), and by increased OXTR expression in the medial preoptic area (375). As a result, OXT neuronal activity, peripheral secretion of OXT into blood (157, 237), and OXT release within the brain, e.g., within the PVN of rats (1071), are highly stimulated. In turn, peripheral and central OXT essentially promotes copulation (26, 374, 1057). Thus central infusion of OXT induced penile erection, whereas infusion of non-selective OXTR and V1a antagonists inhibited male copulatory behavior in rats (25, 27).

Projections of parvocellular OXT neurons to the spinal cord provide the neuroanatomical basis for these effects (372). The PVN is further connected with the corpus cavernosum, penile muscles, epididymis, and prostate of male rats, as shown by tract-tracing studies using pseudorabies virus injections in the respective tissue, which is retrogradely transported (372). The putative PVN OXT neurons projecting to the spinal cord have collateral projections to the nucleus paragigantocellularis in the brain stem, which exerts a tonic serotonergic inhibition of penile reflexes (770). The functional circuitry is completed by magnocellular OXT neurons in the PVN, which receive sensory inputs from the penis and become activated upon sexual stimulation (770). Thus, within this circuit, sensory information related to sexual cues activates magnocellular OXT neurons, which release OXT into blood and within the PVN (1071), and such local OXT may trigger activation of nearby parvocellular OXT neurons (539), which project to the spinal cord to promote genital reflexes (1058).

Extensive pharmacological manipulation of the brain OXT system provided convincing evidence for an essential role of brain OXT in erection, copulation, and ejaculation, which has recently been reviewed (26, 1057). Briefly, icv infusions of OXT increased non-contact erections (observed in the presence of an inaccessible receptive female) and reduced the latency and intervals of ejaculations in rats (27). Similar effects were observed in dominant, but not subordinate, squirrel monkeys (1098). In contrast, central infusion of an OXTR antagonist inhibited male sexual behavior by increasing the latency to first intromission, generally decreased copulatory activity, and abolished ejaculation (25, 28, 32, 689). In support, selective lesion of parvocellular PVN neurons reduced the number of OXT-immunoreactive fibers to the lumbosacral spinal cord and resulted in impairment of various aspects of copulatory behavior (7, 628).

More detailed studies with the aim of localizing OXT effects on male sexual behavior revealed increased erection after intrathecal infusion at the lumbo-sacral, but not thoraco-lumbar, level of the spinal cord (381). Moreover, infusion of OXT into the PVN, hippocampus, ventral tegmental area, or postero-medial amygdala facilitated non-contact erections (176, 688, 690). Positive local effects on the frequency of mounting, ejaculation latency, and post-ejaculatory intervals were also found after micro-infusion of OXT into the medial preoptic area (374, 375). In most of these brain areas, an OXTR antagonist could block or at least attenuate the described OXT-induced effects. Interestingly, when sexually sluggish and sexually efficient male rats were compared, OXTR binding within the medial preoptic area was lower in the latter, which is likely the consequence of elevated local OXT release, high availability of OXT in the extracellular fluid, and downregulation of OXTR expression (see sect. V*D*). In contrast, acute mating increased OXTR mRNA, and OXTR protein levels within the medial preoptic area were found to be higher in experienced males (374, 814).

OXT may also be essential for sexual satiety effects following orgasm by flooding OXTR in relevant brain regions, such as the nucleus accumbens, resulting in their desensitization (1057).

In addition to the profound involvement of OXT in the regulation of male sexual behavior at the brain level, OXT circulating in blood is likely to contribute to these effects by directly acting on male reproductive organs; the more so as OXTR are expressed in the male genital organs (see **TABLE 2**). In line with this, OXT concentrations in plasma or human saliva were found to increase during orgasm in men, and during mating or sexual interactions in rats and rabbits (157, 237, 447, 565, 973, 1033). Peripheral OXT was described to facilitate ejaculation as measured in rats, rabbits, and bulls (30, 32, 33, 687, 796, 973), but may even attenuate erection (1135), which is in contrast to its central actions (see above) (192). These effects are likely mediated by OXTR located in the testis, epididymis, ductus deferens, prostate, and penis, resulting in increased contractility of smooth muscle cells involved in ejaculation (204). Nevertheless, injection of the non-peptide OXTR antagonist epelsiban (GSK557296), which easily crosses the blood-brain barrier, was most effective in inhibiting ejaculation when infused icv or intrathecally at the lumbar level, but less after iv or thoracic level, pointing toward a predominant central/neuronal level of OXT action (191).

2. Interaction of OXT with other neurotransmitters in the regulation of male sexual behavior

OXT interacts with many neurotransmitters in the regulation of male sexual behaviors. For example, the pro-erectile effects of OXT are supported by dopamine, glutamate, and nitric oxide within the PVN as well as in the hippocampus, amygdala, and ventral tegmental area. In contrast, GABA, opioid peptides, melanocortin (alpha-MSH), and endocannabinoids rather inhibit the pro-sexual activity of OXT neurons (for review see, Refs. 26, 820, 1057).

Interactions with 5-HT in the context of sexual behavior seem to be particularly complex (for review, see Ref. 961). 5-HT inhibits sexual functions and increases the ejaculatory threshold via activation of 5-HT1B/2C receptors (239), whereas activation of 5-HT1A receptors facilitate ejaculation (961). 5-HT and OXT interact in various brain areas associated with male sexual behavior, such as the PVN, where 5-HT1A receptors are expressed by OXT neurons (1136). In the medial preoptic area, local OXT facilitated, whereas 5-HT inhibited, male sexual behavior (279, 374). In general, OXT and 5-HT importantly balance sexual activity and male sexual behavior by partly exerting opposing effects. These fine-tuned interactions between the OXT and 5-HT system have to be kept in mind, since alterations in 5-HT levels in the extracellular fluid can be achieved, for example, by administration of selective serotonin reuptake inhibitors (SSRI), a class of antidepressive drugs. Chronic SSRI treatment may result in delayed ejaculation, and it is currently believed that the differences between the various SSRIs in inducing ejaculation delay are related to gradual desensitization of 5-HT1A receptors on OXT neurons (for review, see Ref. 239).

3. Female sexual behavior

In females, sexual behavior consists of the two main components: proceptivity and receptivity, which are partly under the control of OXT (97). During proceptivity and first interactions with the male, the estrous female will start to display soliciting, proceptive behavior ("hopping" and "darting") to attract the attention of the male and to induce arousal (1058). Proceptive components also include the investigation of male genitals, vocalizations, exposure of own body parts, and ephemeral physical contacts. However, lordosis, the receptive dorsal-flexed posture displayed by the estrus female in a fixed standing position, is the most important copulatory behavior in females to allow male intromission (1057). As found in males, both magno- as well as parvocellular OXT neurons of the hypothalamic PVN were shown to become activated by sexual activity in females, as indicated by the expression of the immediate early gene product Fos (148, 342, 829, 1112). Consequently, OXT is secreted from the neurohypophysis into the periphery as reflected by increased plasma levels in sheep during vagino-cervical stimulation (519) and by increased OXT concentration in saliva found in women during sexual self-stimulation (85, 237). However, sexual stimulation also triggers OXT release in various brain regions. During vagino-cervical stimulation of ewes, an increased OXT release was found within the olfactory bulb (518). During mating, OXT is also released within the hypothalamic PVN of female rats (773), and the nucleus accumbens of female monogamous

prairie voles (886). However, in female rats, the central release of OXT was found to depend on the mating conditions; we could show that the control of mating by the female (i.e., paced mating) is required to trigger central OXT release (and to avoid an increase in anxiety after mating); accordingly, non-paced mating and absence of female control did not stimulate intracerebral OXT release (773). Somatosensory information from the female reproductive organs may reach and activate OXT neurons via the pelvic nerve as well as vagal nerve (97, 548, 713). However, regarding the elevated peripheral levels of OXT during arousal and orgasm in females, it still seems unclear whether OXT increases sexual arousal or is a natural by-product of it (97).

It is well established that brain OXT has profound effects on lordosis and orgasm in females. These effects are strongly dependent on interactions with female sex steroids, i.e., estrogens and progesterone, and can only be seen after steroid priming, mostly performed in ovariectomized rats. Two brain regions seem to be of particular importance as target for OXT to modulate female sexual behavior: the ventromedial hypothalamus and medial preoptic area; infusion of OXT icv or directly into the ventromedial hypothalamus stimulated proceptive and lordosis behavior (679, 807), whereas infusion of an OXTR antagonist icv into the ventromedial hypothalamus or medial preoptic area before treatment with progesterone decreased lordosis posturing and inhibited female sexual behavior in rats (806). Comparable effects were reported after peripheral administration of OXT in primates (90). Therefore, it is likely that OXT acts on peripheral OXTR localized in pelvic organs involved in (pre-)copulatory behavior (770) to modulate somatosensory inputs. In addition, OXT fibers descend into the lumbo-sacral parts of the spinal cord (128, 985). Supporting the role of OXT in female sexual behavior in rats, McCarthy and colleagues showed that infusion of antisense oligodeoxynucleotides targeting the *Oxtr* (to reduce OXTR synthesis) into the ventromedial hypothalamus of estrogen-primed females blocked female receptivity (679).

It is of interest to note in this context that only one detailed behavioral study on the consequences of *Oxt* gene knockout revealed deficits in female sexual behavior. Specifically, an increase in the frequency and duration of non-receptive postures and a decrease in receptive postures were reported in *Oxt* knockout mice (1146). This finding is in contrast to previous reports on the sexual capacity of *Oxt* knockout mice (764, 1123). *Oxt* gene knockout was also accompanied by reduced expression of the *OXTR*, $V_{1a}R$, and estrogen receptor α and β in various brain regions (1146).

Altogether, OXT seems indispensable for efficient female sexual behavior both in mice and rats, indicating that these functions are evolutionary conserved.

4. Interaction of OXT with other neurotransmitters in the regulation of female sexual behavior

As mentioned above, both estrogen and progesterone are essential for the promotion of female sexual behavior by OXT (339). Female sex steroids induce OXTR synthesis in the ventromedial hypothalamus (see sect. V; Ref. 922), thus modulating local OXT binding and OXT signaling. Interestingly, a high proportion of ERα-immunoreactive neurons within the ventromedial hypothalamus co-express OXTR (259), giving further support to the essential interactions between OXT and female sex steroids in female sexual behaviors.

Classical neurotransmitters were also shown to interact with OXT in the control of female sexual behavior and to be present in OXT-fibers (339, 678). OXT neurons are capable of co-releasing glutamate within or close-by the ventromedial hypothalamus, and glutamatergic agonists were shown to exert a local inhibitory effect on female sexual behavior (371, 677, 678). Glutamate and steroid interactions are also present in the ventromedial hypothalamus contributing to the complexity of fine-tuned female sexual behavior.

5. OXT and sexual behavior in humans

Besides the finding of increased OXT plasma concentrations during sexual arousal and orgasm in both men and women (see above and Refs. 85, 158, 237, 727, 778), there is only one study monitoring central OXT concentrations during sexual behavior in humans using a serial CSF sampling method (566); however, CSF OXT (as well as AVP and prolactin) remained unchanged, whereas CSF norepinephrine increased during masturbation in healthy men. Nevertheless, several studies demonstrated effects of i.n. OXT on related physiological and behavioral parameters mostly studied in men. Thus, after i.n. OXT, men were faster to detect the valence of positive stimuli conceptually associated with sexuality, bonding, and social relationships (1038) and had augmented epinephrine plasma responses to sexual activity (135). In addition, i.n. OXT increased the intensity of orgasm and contentment following sexual intercourse in heterosexual couples (67). In this study, men additionally indicated higher levels of sexual satiety after sexual intercourse; women felt more relaxed or indicated better abilities to share sexual desires. However, i.n. OXT did not alter "classical" parameters of sexual function, such as sexual drive, ar,ousal or penile erection and lubrication (67).

B. Social Bonding/Pair Bonding

The phenomenon of pair bonding, i.e., the selective preference for a particular mate, can only be found in ~4% of mammalian species. Remarkably, pair-bonded monogamy

has been explicitly associated with the development of larger relative brain sizes, when comparing, for example, pair-bonded and non-pair-bonded species of bats and carnivores (295). This implies that it may have been the complex social and cognitive demands of pair bonding that contributed to the development of large brains in mammals.

The North American prairie vole (*Microtus ochrogaster*) has become an important animal model for investigating the role of OXT, and also of AVP, in pair-bonding behavior (164, 475, 1096, 1121). The prairie vole is a monogamous, biparental rodent, which exhibits enduring pair bonds characterized by selective affiliation, i.e., partner preference, and aggression against other conspecifics after mating. The importance of brain OXT in pair bonding, especially in female voles, has been demonstrated by a conclusive chain of evidence. First, species-dependent differences in regional OXTR and AVPR expression were found to form the neuroanatomical basis of monogamy. Higher OXTR densities have been revealed in the nucleus accumbens and caudate putamen of female (475) as well as male (787) prairie voles compared with relatively asocial, non-monogamous vole species such as the montane vole (*Microtus pennsylvanicus*). In addition, the expression of the AVPR subtype V1AR in the medial amygdala, ventral pallidum, and mediodorsal thalamus was higher in monogamous prairie voles compared with non-monogamous species (476). This implies that the variable expression of OXTR and AVPR in specific brain regions may be an important mechanism in evolution of species-typical differences in social bonding and affiliative behavior. Moreover, icv infusion of synthetic OXT induced partner-preference in female prairie voles without prior mating (164), whereas infusion of an OXTR antagonist into the nucleus accumbens prevented mating-induced partner preference formation both in female (1121) as well as male (494) prairie voles.

Further evidence for an involvement of OXT in pair bonding was provided by a preliminary study using RNA interference to knock down selectively the OXTR in the nucleus accumbens of female prairie voles. Infusion of an adeno-associated viral vector expressing a short hairpin RNA targeting *Oxtr* mRNA resulted in reduced density of OXTR in the nucleus accumbens of female prairie voles and impairment of both alloparental behavior and partner preference formation (513). Along the same line, increasing OXTR density in the nucleus accumbens using viral vector gene transfer was found to accelerate the formation of a partner preference in female prairie voles (886).

With respect to the gender-specific involvement of OXT and AVP and their receptors in female and male pair bonding in prairie voles, respectively, it originally appeared that OXT is essential for female pair bonding, whereas AVP is crucial for male alloparental behavior and partner preference (182, 1096). However, accumulating evidence summarized above supports the view that OXT plays a crucial role in pair bonding in males as well (182, 494, 787, 1121).

Consistent with the hypothesis that mating, affiliation, and partner preference are highly rewarding (23, 471, 627), OXT seems to significantly contribute to conditioned reward learning (1121). Axon collaterals of magnocellular OXT neurons in the PVN and SON project to the nucleus accumbens and may release OXT during mating, as shown in a few female voles (885). Subsequently, locally released OXT may act on dense local OXTR and strongly interact with the local dopaminergic system, which becomes highly activated by mating (627). Consequently, the rewarding and hedonic properties of mating may become coupled with olfactory cues of the mate, resulting in conditioned partner preference and pair bonding (1121).

Moreover, OXT signaling in the brain, which is reinforced by mating and, in the presence of the partner, is important for emotional stability and facilitation of active stress coping styles, opposing depression-like behaviors. Indeed, separation from the partner prairie vole for a few days resulted in passive stress coping (103) and severely impaired central OXT signaling at several neuronal levels, as described in detail below (see sect. VIII*E*) (100).

Another aspect of social behavior mediated by brain OXT in the context of pair bonding is consolation behavior. Consolation behavior and empathy were thought to have been established only in primates, elephants, and other developed mammals with the evolution of advanced cognitive capacities (245, 841). However, Burkett et al. (134) recently showed that pair-bonded voles display increased grooming behavior toward the partner during their reunion after the partner had repeatedly experienced an extremely stressful situation in isolation. This has been interpreted as consolation behavior and has been shown to be dependent on OXTR-mediated signaling within distinct brain regions. Infusion of an OXTR antagonist into the anterior cingulate cortex, where abundant OXTR were identified in prairie voles, blocked the consolation behavior of the partner (134).

1. OXT and pair bonds in humans

The few human studies on OXT and pair bonding support the notion of OXT promoting partner interactions and social relationships (for review, see Refs. 465, 695). Thus, compared with singles, basal concentrations of OXT in blood were described to be increased in couples during the early stages of romantic love and stay significantly elevated in couples remaining together 6 mo later (919).

Moreover, i.n. OXT motivated pair-bonded, but not single, men to keep a greater distance between themselves and an attractive female stranger, but only under very specific ex-

perimental conditions (e.g., presence of a female, but not male, experimenter, in the experimental room, who was not moving). The same results were confirmed under photograph-based test conditions (917). Interestingly, viewing the face of a romantic partner activated reward-associated regions such as the ventral tegmental area and nucleus accumbens (2, 58). In healthy pair-bonded men, i.n. OXT further increased the neural responses in the VTA and nucleus accumbens when viewing pictures of the female partner's face but not when viewing pictures of an unfamiliar woman. This effect was paralleled by a more favorable perception of attractiveness of the female partner (918). Viewing pictures of the romantic partner also reduced self-reported thermal pain (1124).

Collectively, these data in men suggest that OXT may rather contribute to romantic bonds and the maintenance of an already established pair bond rather than to promote a new partnership. This is partly controversial to the role of OXT in prairie voles, where the peptide has mostly been described to be necessary for the formation of new pair bonds (see above).

2. OXT and other forms of social bonds

In addition to pair bonding, complex bonds are found, e.g., among non-human primates, which form strong, enduring social bonds, especially between genetically related individuals (925, 935). These relationships are defined by high rates of cooperative behaviors including grooming (921), and have been associated with general fitness and reproductive benefits (147, 936). As seen in other animals showing bonding behavior, the general (re)activity of the OXT system also seems to contribute to social bonds in primates, although direct evidence is limited. In chimpanzees, urinary OXT concentrations reflecting magnocellular OXT neuronal activity and peripheral OXT secretion were higher after grooming in bond partners compared with non-bond partners (212). Also, peripheral administration of OXT to social, free-living meerkats (*Suricata suricatta*), which live in larger groups, increased rates of several cooperative activities (e.g., digging, guarding, pup-feeding) (654) and decreased hostile and aggressive interactions.

3. OXT and social bonds across species-borders

The ability of OXT to reinforce enduring bonds does not seem to be restricted to monogamous species or to social bonds within members of a given species. OXT was also found to promote individual social bonding outside a reproductive context and even across species borders, for example, between dogs and their owners. Gazing at their owners, domestic dogs responded with elevated urine OXT levels, which correlated with the duration and intensity of dog-to-owner gazing (734, 884). Moreover, it could be shown that i.n. treatment of dogs with synthetic OXT increased dog gazing behavior toward their owner, who, in turn, responded to this intense social interaction with elevated OXT secretion as assessed in urine samples. These findings implicate an OXT-mediated positive social loop between domestic dogs (but not hand-raised wolves) and their owners.

Although it is difficult or almost impossible to show directly, there is no doubt that intense and individual social interactions (such as gazing between the dog and its owner) result in intracerebral release of OXT within distinct brain regions. An indication of this possibility is the finding that simple social exploration and interactions, i.e., sniffing at a same-sex conspecific, increased OXT release within the lateral septum in mice, as assessed by microdialysis (1148). Another likely brain target of OXT in the context of close social interactions is the reward circuitry, since intense social interaction with your own dog is highly rewarding, thus increasing the motivation to do so. Intranasal OXT also promoted social motivation to approach and interact with other same-sex dogs and with human partners, which is the basis for the formation of stable social bonds (884).

C. Regulation of Maternal Care and Aggression

Maternal behavior is common to all mammals, although to various degrees. It includes maternal care of the young as well as their protection based on the strong attraction between a mother and her infant(s). This is in strict contrast to the relatively few species displaying pair bonding, i.e., bonding between adult opposite sex conspecifics. Under the influence of hormonal fluctuations during pregnancy, profound adaptations of the maternal brain were described (126, 748, 772, 951), which also severely affect the activity of neuropeptides such as OXT (see below), AVP (105, 588, 1073), CRF (540, 619, 1073), and prolactin (1019), which are all important mediators and regulators of maternal behavior (for review, see Refs. 630, 951).

1. High activity of the OXT system peripartum

The behavioral adaptations seen at the end of pregnancy and in lactation are directly associated with the increased activity of the OXT system. In the first instance, the elevation of hypothalamic OXT synthesis (1147) contributes to an increased availability of OXT in magnocellular neurons to meet the demands of increased neurohypophysial OXT secretion and elevated OXT concentrations in blood during birth and lactation. In addition, the increase in OXT synthesis is also the prerequisite for higher levels of OXT release within several hypothalamic and limbic brain regions in response to parturition- and suckling-related stimuli (see sect. IV) (517, 520, 586, 714, 743). In this context, a higher number of OXT-positive fibers were found within the lateral septum of lactating mice (692a). Higher levels of

OXTR expression and OXTR density within many brain regions such as the PVN, BNST, septum, hippocampus, medial preoptic area, ventral tegmental area, or olfactory bulb further contribute to the high activity state of the brain OXT system peripartum (107, 166, 685, 1046). As a consequence of increased availability of both OXT in the extracellular fluid as well as local OXTR, neuronal OXTR-mediated signaling cascades were described to become highly activated during lactation, as studied in detail in the hypothalamic PVN (500).

Recently, the expression of the oxytocinase enzyme (placental leucine aminopeptidase) in magnocellular OXT neurons of the SON and PVN was found to be higher in lactating compared with pregnant or virgin rats (1009). This enzyme is mainly expressed peripherally, where it promotes and controls OXT degradation in the uterus, placenta, and plasma during pregnancy. Inhibition of central enzyme activity by icv infusion of amastatin increased the frequency of reflex milk ejections in lactating dams during suckling, indicating its role in the regulation of auto-excitatory OXT actions during the milk-ejection reflex (1009). However, its role in in the fine-tuned regulation of OXT-mediated behaviors peripartum remains to be elucidated.

OXT-dependent behavioral adaptations peripartum include many aspects of maternal care, maternal aggression, improved spatial memory, offspring recognition including sensitive auditory processing of offspring vocalization, reduced anxiety and fear-responses, and an attenuated neuroendocrine stress response (for review, see Refs. 104, 748, 772, 951). The simultaneous activation of peripheral and central OXT systems is a wonderful biological example for the synergistic action of a neuropeptide acting in two distinct compartments of the body. Circulating in the periphery and acting on OXTR abundantly expressed in myometrial and myoepithelial cells, OXT facilitates the birth process and provides milk for the young, respectively. In the brain, OXT promotes the essential behavioral adaptations of the mother promoting the onset and maintenance of complex maternal behaviors and mother-offspring bonds. Both physiological and behavioral aspects of OXT functions are essential for the survival of the young in mammals. Moreover, the anxiolytic and anti-stress effects of OXT, which are particularly pronounced peripartum (951), contribute to the optimal preparation of the mother for motherhood.

2. Maternal care and mother-infant bonding

In some mammals, including primates and ungulates such as sheep, horses, or elephants, there exist strong, enduring, and selective mother-offspring bonds based on an individual recognition processes. For example, sheep form selective bonds with their individual offspring within 2 h of giving birth based on the formation of an individual olfactory memory. This allows the ewe to distinguish her own lamb from others of the herd, which she will consequently reject. The development of a mother-infant bond consists of a two-step process: a recognition process and a persistent attraction process (772). The following studies provide evidence that brain OXT is important for both aspects.

In ewes, OXT is released within the olfactory bulb, medial preoptic area, BNST, and substantia nigra during birth and suckling (517, 520). These brain regions form essential components of the neural circuitry regulating maternal behavior (772). Central infusion of OXT into estrogen- and progesterone-primed sheep site-specifically promoted maternal behavior. Whereas, in the PVN, synthetic OXT induced full maternal responses (219), only partial maternal responses, i.e., reduced aggression toward another lamb, were found after infusion into either the olfactory bulb or the medial preoptic area (516). Within the olfactory bulb, OXT orchestrates individual social memory (272; see below) and thus may promote individual lamb recognition. These site-specific effects suggest that simultaneous or at least coordinated OXT release in these OXT target regions during birth, suckling, and/or mother-lamb interactions are essential for full maternal responsiveness and lamb recognition.

Such individual bonds are lacking in rat and mice dams, which give birth to altricial young. However, the performance of intense maternal behavior, including care for and defense of pups, is crucial in those species that give birth to relatively undeveloped offspring. As mentioned before, both OXT release within the SON and PVN as well as extra-hypothalamic release of OXT within the septum and dorsal hippocampus were found during birth and/or suckling in lactating rats (see sect. IV). However, whether such local release is the consequence of physiological stimuli associated with the Ferguson reflex and the milk ejection reflex, respectively (716), or directly linked to the performance of maternal behavior remains to be studied.

Pharmacological evidence for the role of OXT in maternal behavior has also been provided in rodents. In steroid-primed virgin female rats, short-latency maternal responses were found after icv infusion of OXT (809). In support, infusion of an OXTR antagonist into the cerebral ventricles or directly into the medial preoptic area or lesion of the PVN (the major source of brain OXT) delayed both the onset of maternal behavior, i.e., pup retrieval and assuming a nursing posture over pups after birth and during lactation (474, 808, 1046) as well as ongoing maternal behavior (105). Chronic icv infusion of OXT, starting on *lactation day 1*, increased the frequency of arched back nursing over 5 consecutive days in those rat dams, which showed a relatively low level of maternal care before treatment (105). Despite the fact that bilateral infusion of an OXTR antagonist into the medial preoptic area impaired maternal care, local OXT release was found unchanged during the perfor-

mance of maternal behavior (104). Therefore, the robust increase in OXTR expression also found in the medial preoptic area during lactation (685) might provide the basis for the fine-tuned regulation of maternal care, even under relatively constant levels of local OXT in the extracellular fluid (107).

In addition to the medial preoptic area, OXT actions within the ventral tegmental area seem to be important for maternal behavior, since local OXTR binding is highest around parturition (808). Although, in parturient rats, local infusion of an OXT antagonist ([d(CH2)5,O-Me-Tyr2,Thr4, Tyr9,Orn8]-vasotocin (304) delayed this behavior (808), local OXT infusion in estrogen-primed virgin female rats stimulated the onset of maternal care (316). Furthermore, OXT release and binding within the dorsal hippocampus (741) have been linked to maternal behavior in the context of memory processes, especially in spatial memory. In lactating mice, OXT was found to promote long-term spatial learning, which is likely mediated by OXTR-stimulated elements of MAP kinase cascade, CREB phosphorylation, and generation of profound long-term potentiation within the hippocampus (see sect. VI). This is an important finding, since an improved hippocampus-dependent learning and memory, and possibly an improved spatial memory during motherhood, may help the dam to return to the nest after searching for food at more distant locations (1011).

In an elegant study, Marlin et al. (670) could demonstrate another aspect of maternal behavior regulated by OXT in mice, using optogenetic stimulation of OXT neurons within the PVN. After viral transfection, those neurons express a specific channel rhodopsin variant under the control of the *Oxt* gene. Optogenetic, i.e., blue light stimulation of these PVN neurons, reduced the latency of virgin female mice to become maternal. They also described lateralization of the OXTR expression in the left auditory cortex, which they found essential for the initiation of pup retrieval behavior induced by ultrasonic vocalization of the pups. In addition, the left auditory cortex proved to be part of an OXT-sensitive circuitry for the onset, but not maintenance, of maternal behavior (670). Here, OXT may increase neuronal sensitivity, thereby transforming weaker behavioral responses in virgins into more robust maternal responses postpartum.

Recently, a cluster of potential dopaminergic neurons in the anteroventral periventricular nucleus of the hypothalamus was revealed as another neuroanatomical mechanism contributing to the OXT-mediated control of maternal behavior in mice. These neurons relay a monosynaptic input to OXT neurons in the PVN, but not SON, and may project to other relevant regions such as the medial preoptic area. Upon stimulation of these neuronal clusters by optogenetic means, OXT neurons became activated, resulting in increased OXT levels in blood as well as in a higher maternal responsiveness (922a).

Another aspect of maternal care deserves attention in the context of OXT actions, i.e., licking and grooming of the pups. Naturally occurring variations in maternal licking and grooming were found in Long-Evans rats and were related to the expression of the OXTR. Females that were more maternally responsive to pups and that showed increased levels of pup licking/grooming also showed higher OXTR levels, for example, in the PVN, medial preoptic area, lateral septum, central amygdala, and BNST. Infusion (icv) of an OXTR antagonist to high licking/grooming mothers abolished the differences in pup licking and grooming, suggesting that OXT and OXTR are functionally related to this specific component of maternal behavior (169, 350).

In other brain regions, such as the medial preoptic area, ventral tegmental area, and nucleus accumbens, OXT was found to boost maternal motivation and attraction to the young. For example, within the nucleus accumbens, OXT interactions with dopamine promote and sustain maternal attraction to the young throughout the entire postpartum period, also in absence of peripartum hormone fluctuations (772). Furthermore, in the substantia nigra as part of the basal ganglia and the motoric system, OXT is likely to promote the quiescent posture of the mother essential for allowing the offspring to suckle; in rats and mice, arched back nursing describes this posture best (104).

The described findings in sheep, rats, and mice provide substantial evidence for OXT being central to the onset and maintenance of, and motivation for, maternal behavior. However, this view was initially challenged by the finding that OXT knockout mice had no obvious dysfunctions in maternal behavior [except they could not provide milk due to the lack of functional milk ejection reflexes (764)]. However, C57Bl6 mice, from which the knockouts are originating, are spontaneously maternal in the presence of pups (1123). Later, more-detailed behavioral observations revealed impaired pup retrieval and reduced pup licking in nulliparous OXT knockout mice (811). Moreover, OXTR knockout mice showed an increased latency until the initiation of maternal care, whereas no differences in other aspects of maternal care could be identified (867), further supporting the essential role of OXT for the establishment and fine-tuned maintenance of maternal behavior.

3. Maternal aggression

An important aspect of maternal behavior is maternal aggressive behavior of the lactating animal directed against any threat toward the offspring. In laboratory rodents, maternal aggression can be assessed during the maternal defense test. During the test, either a male (631) or a virgin female (758) intruder is placed into the home cage of the lactating resident, taking into account that the intensity of maternal aggression increases dramatically in postpartum rats due to hormonal fluctuations (166).

The involvement of OXT in the regulation of maternal aggression is still partly contrasting, since the effects seem to be species- and brain region-dependent, and dependent on the treatment schedule as well as on the innate state of maternal aggression of the lactating animal studied (99). For example, in rats selectively bred for low (LAB) vs. high (HAB) anxiety-related behavior, which display low and high maternal care and maternal aggression levels, respectively (102), chronic icv administration of OXT increased maternal aggression in LAB, whereas chronic icv infusion of the OXTR antagonist reduced the defensive response of HAB dams (104). In contrast, in non-selected Wister rats, acute icv infusion of an OXTR antagonist did not alter maternal aggression toward the virgin intruder rat (758). Furthermore, differences in the availability of endogenous OXT, e.g., within the PVN and the central amygdala, were found to contribute to differences in maternal aggression in HAB and LAB dams (101, 102), and local OXT release was found to correlate with the level of maternal aggression. Both within the PVN and central amygdala, bilateral blockade of OXTR by local retrodialysis of an OXTR antagonist decreased the aggressive behavior in HAB dams (102). In support of the role of OXT in the central amygdala promoting maternal aggression, repeated local administration of OXT enhanced maternal aggression toward the male intruder in lactating hamsters (332). In contrast, OXT infusions bilaterally into the central amygdala of rat dams were found to reduce some aspects of maternal aggression, such as the frequency of biting and frontal attack (199). With respect to the PVN, bilateral electrolytic lesion of the PVN reduced the frequency and duration of attacks in rats, indicating impaired maternal aggression (200).

OXT may also act within the BNST to regulate maternal aggression in the lactating dam, and more as local OXTR are upregulated during lactation (106, 166, 685). However, infusion of synthetic OXT into the BNST before the maternal defense test lowered the frequency of biting the male intruder rat (199).

Thus, although the available studies support a general role of brain OXT in the promotion of maternal aggression, final conclusions about the brain regions involved are not yet tangible.

4. OXT and caregiving behavior in humans

Studies conducted in human parents indicate that OXT potentially affects parenting and infant-caregiving styles. According to one study (323), baseline plasma OXT concentrations during pregnancy predict postpartum attachment of the mother to the child, more specifically, soft hugs, caresses or baby talk by mothers, and tossing the baby (387). More than baseline levels, differences in stimulus-dependent release of OXT into blood predicts the mother's response to the child's needs and her readiness for social reciprocity (977). In contrast to the hypothesis of a positive correlation between plasma OXT levels and attachment style, urine OXT levels in mothers who play with unfamiliar children were described to be higher than in mothers who play with their own children (80). To which extent stress factors contribute to this finding remains to be shown. Preliminary data also reveal correlations between CSF or urine OXT concentrations and early life adversity or trauma in children and mothers (359).

Synthetic OXT applied i.n. was found to affect maternal-infant or paternal-infant interactions. For example, i.n. OXT-treated fathers exhibited longer episodes of touch and gazed at their child faster with reciprocal effects on the child's social behavior (321). In this context, it would be of interest to examine whether OXT secretion, as assessed, for example, in saliva is increased in non- or placebo-treated fathers during interactions with their child.

D. Regulation of Inter-Male and Inter-Female Aggression

1. OXT and rodent aggression

Since OXT promotes essential affiliative behaviors described above, the question arose to which extent OXT is involved in the regulation of aggressive, antisocial, or egocentric behaviors. In mammals, aggressive behaviors are important for the defense of offspring (see above) but also to fight for territory, food resources, and attractive mating partners. In laboratory animals, especially rats and mice, the resident-intruder test is most often used to quantify inter-male (553, 759), and also inter-female (236), aggressive behavior. In these standardized tests, the experimental animal (the resident) is confronted with a slightly smaller same-sex conspecific intruder in the resident's home cage where it had established its home cage territory. The latency until the resident first attacks, the amount of aggressive behaviors, as well as qualitative aspects, such as ferociousness of attacks and attacks of vulnerable body parts, are scored.

Generally, in contrast to AVP, the involvement of the brain OXT system in rodent aggression is rather understudied. In wild-type Groningen rats, high inter-male aggression was associated with reduced OXT synthesis in the PVN, but not SON, and increased OXTR binding in the central amygdala and BNST (144). Similarly, in virgin female Wistar rats that displayed aggressive behavior and attacked the female intruder, we found a lower level of activation of OXT neurons (using pERK1/2 as a co-marker) compared with females that tolerated the intruder (236). Likewise, in the eusocially organized naked mole rat (*Heterocephalus glaber*), exposure to an intruder increased the activation of OXT neurons in the PVN in non-aggressive worker males but not in aggressive soldier males (426). It is interesting to note that the higher activation of the brain OXT system in

socially tolerant compared with rather aggressive individuals was not reflected by increased OXT concentrations in blood (297, 1025).

Indications for a role of endogenous OXT in aggression also come from studies using environmental manipulations early in life, which have long-lasting effects on various emotional and social behaviors. As such, the maternal separation paradigm (3 h of daily separation of the pups from the mother during the first 2 postnatal weeks), which has been mainly used in rats (779, 828, 1088) and mice (800, 882), resulted in increased intermale aggression (1055, 1056; for review, see Ref. 413). Although hypothalamic OXT synthesis was not altered, maternal separation resulted in reduced OXTR binding in the caudate putamen and lateral septum, and elevated binding in the medial preoptic area in adult male Wistar rats (646). However, whether increased OXTR binding indeed reflects reduced OXT neurotransmission (due to reduced availability of the ligand in that brain area; see above and Ref. 1148) still needs further investigation.

An opposite effect of early life stress was described in adult male mice, in which a reduced inter-male aggression was accompanied by an increased number of OXT-immunoreactive neurons in the PVN (1032). This is again in support of the hypothesis that brain OXT rather suppresses male aggressive behavior.

To characterize the possible link between the endogenous OXT system and aggression, intracerebral microdialysis has been performed during ongoing behavioral testing in the resident-intruder test. Whereas intracerebral release of AVP has been monitored in various brain regions during the display of aggression (1054; for review, see Ref. 759), there is only one preliminary report about the central release of OXT in males and virgin females. Thus OXT release in the PVN was found to be increased in male rats during aggressive encounters with an intruder, but the amount of OXT detectable in the 30-min dialysates did not correlate with the extent of aggression (238). In contrast, in trained virgin female rats, which generally display a low amount of aggression, levels of OXT release within the PVN were relatively low; nevertheless, the increase in local OXT correlated negatively with the duration of aggression (238).

These studies support the assumption that brain OXT rather exerts an inhibitory effect on aggressive traits and acute inter-male and inter-female aggression. Studies using male *Oxt* or *OXTR* knock out mice only partly support this view, since both an increase as well as a decrease in aggression were reported in mice lacking OXT (243, 596, 852, 1097). These differences were explained by the different breeding protocols, since in some studies Oxt knockout mice were born to conditional Oxt knockout mothers, whereas in others they were born to heterozygous Oxt mothers. The latter condition, however, allowed transient exposure of Oxt knockout offspring to maternal OXT during gestation and lactation, which may impact on the level of aggression in adulthood (262, 991). In contrast, consistently increased levels of aggression were observed in the complete absence of OXTR in Oxtr knockout mice (262, 429, 898, 899, 991). However, in case the *Oxtr* knockout was induced after weaning rather than at fertilization and was limited to forebrain areas, the effect on inter-male aggression disappeared (262). Limiting the ablation of *Oxtr* to serotonergic neurons in the dorsal and median raphe nucleus, on the other hand, reduced male aggression (795).

In line with the above-mentioned assumption on the role of endogenous OXT, central infusion of synthetic OXT was reported to inhibit aggression in male and female rats independent of the route of administration and the dose used (between 1 and 1,000 ng icv) studied so far. For example, acute icv infusion of OXT reduced inter-male aggression in both male wild-type Groningen rats (143) as well as in virgin Wistar rats (236). Similarly, in male mice (C57Bl/6), acute icv infusion of OXT reduced aggression after cohousing with unfamiliar male conspecifics, whereas an OXTR antagonist had the opposite effect (24). Interestingly, a similar effect on inter-male aggression was found in socially isolated and high aggressive C57Bl/6 mice after i.n. administration of OXT (508). In support of an anti-aggressive effect of OXT, steroid-primed female prairie voles treated icv with OXT also displayed reduced female-to-male aggression (1099). In contrast, in male prairie voles, male-to-female aggression was not affected by OXT (657, 1099), and chronic icv infusion of OXT over 24 h did not affect mating-induced aggression of male prairie voles against male intruders (1096). In male squirrel monkeys, acute OXT was reported to even increase aggressive behavior but only in dominant, but not in subordinate, males (1098).

The few attempts to localize the anti-aggressive effects of OXT within the brain revealed the central amygdala in male rats (145) and the medial preoptic area and anterior hypothalamus in virgin female Syrian hamsters (423) to play a prominent role.

Although we can conclude from the partly controversial results summarized above of a general anti-aggressive effect of OXT, more research into the gender- and the species-dependent role of endogenous vs. synthetic OXT in the different aspects of defensive vs. offensive aggression is needed.

2. OXT and human aggression

In humans, *endogenous* OXT has been correlated with parameters of trait aggression, although access to the OXT system is restricted to blood or saliva, indicating peripheral OXT secretion. Only the first of these studies reported a positive correlation between plasma OXT and indirect ag-

gression and irritability (1039); subsequent studies revealed the opposite. For example, plasma OXT concentrations correlated negatively with aggression and positively with empathy in boys with attention deficit and hyperactivity disorder (252). Young adult women with bipolar disorder had lower peripheral OXT levels compared with healthy controls, which correlated negatively with trait aggression (78). Similarly, basal OXT concentrations in saliva correlated negatively with "callous and unemotional traits" in boys with conduct problems (615). Confirming a negative link between aggression and OXT, OXT concentrations in the CSF also correlated indirectly with aggression levels of men and women (603). A similar trend was found in a cohort of female, but not male, suicide attempters, when aggression was specifically assessed (496). It is worth mentioning that OXT-reactive immunoglobulin G and M autoantibodies were slightly elevated in blood of men diagnosed with conduct disorder or convicted of a violent crime compared with healthy men (333), which is most likely associated with reduced OXT activity.

In addition, genetic variations and epigenetic modifications of the *Oxtr* gene have been linked to aggression. Specifically, the level of methylation of *Oxtr* was positively correlated with "callous and unemotional" traits in boys with conduct problems and was negatively correlated with OXT concentrations in plasma (222).

Following the hypothesis that low activity of the brain OXT system is associated with elevated aggression scores in animals and humans, it is obviously tempting to treat aggressive and violent behavior with synthetic OXT, preferably via the i.n. route. So far, the effects of i.n. OXT on aggressive behavior were mainly assessed in various competitive computer games in healthy volunteers, which revealed varying, mostly moderate effects in men and women depending on the specific test conditions. The observed effects reached from no acute effects (12, 13) and modest increase in both reactive and proactive aggression in healthy men and women (738) to decreased aggression in women with higher state anxiety (151). In young adult female patients suffering from a bipolar disorder associated with high trait aggression, i.n. OXT reversed their disorder-induced high threat sensitivity, as reflected by a higher dynamics of eye fixation and increased amygdala reactivity (measured with fMRI) in response to angry faces (77).

A series of studies from De Dreu and his colleagues reported effects of i.n. OXT on parochial altruism, an evolutionary conserved variety of social behaviors, which have strong survival functions (234). In their study, OXT-treated healthy men displayed more in-group trust and in-group love, but did not display more out-group hate and out-group distrust compared with placebo-treated individuals (234). In line with the role of OXT in the defense of offspring and "own genes" (see above), they also showed that i.n. OXT promoted defensive forms of out-group aggression, when out-group threat was eminent. OXT also facilitated in-group conformity and cooperation, while increasing anti-social tendencies toward out-group individuals (235). Interestingly, i.n. OXT modulated the selection of specific allies, which are potentially beneficial during intergroup conflicts to protect their in-group. OXT-treated men considered high-threat targets (faces) as more useful allies and, therefore, selected them more frequently into their team than low-threat targets (233).

In line with a role of OXT to support in-group members and in-group harmony, couples given i.n. OXT manage their conflicts more constructively (269).

Although these results on OXT and aggression support the hypothesis that a "hypo-oxytocinergic state" is associated with an elevated trait aggression and may even predict aggression (662), they do not equivocally support the theory that i.n. OXT treatment is capable of inhibiting aggressive behavior in humans. However, i.n. OXT seems capable of modifying various aspects of complex human social behaviors related to cooperation and support of in-group members. It may shift the individual from being focused on self-interest toward the interests of the members of the in-group.

E. Regulation of Anxiety, Fear, and Stress Coping

Anxiety and depression-related disorders are among the most common psychiatric illnesses, with a high lifetime prevalence of ~30% and 25%, respectively (522) and a high level of comorbidity. Both psychopathologies are characterized not only by severe emotional and stress-coping dysfunctions but also by social deficits such as social withdrawal or social fear, impaired social memory, or various aspects of aggression. The brain OXT system has become a potential target system, e.g., for the treatment of anxiety and fear-related disorders including social anxiety disorder (SAD) and posttraumatic stress disorder (PTSD). This is mainly due to the fact that *1*) the endogenous OXT system responds to anxiogenic and stressful stimuli, *2*) brain OXT is involved in the regulation of anxiety, stress responses, and various social behaviors, and *3*) synthetic OXT exerts robust anxiolytic, anti-stress, and pro-social effects both in rodents and humans (for review, see Refs. 280, 591, 652, 694, 746, 753, 755).

1. OXTR-mediated effects on anxiety and stress responses in animal studies

Stressful, challenging and potentially threatening situations robustly activate the OXT system. The increased neuronal activation has been monitored by electrophysiological means, in situ hybridization and assessment of

OXT mRNA within OXT neurons of the PVN and SON, quantification of OXT secretion into the blood stream by measuring OXT concentrations in plasma or human saliva, as well as monitoring intracerebral release within distinct brain regions using microdialysis as described above. Relevant stressful stimuli, which have been extensively studied in rats and mice in this context, include restraint, forced swimming, shaker stress, social defeat of male rats by an aggressive conspecific, or social defeat of female rats by an aggressive lactating resident dam (maternal defeat) (101, 298, 309, 310, 373, 487, 593, 747, 765, 785, 1088, 1093, 1100; for review, see Refs. 312, 591, 750).

However, no obvious differences in the brain OXT system were detectable in individuals with either high or low trait anxiety. Neither the expression of *Oxt* or *Oxtr* within the brain, nor the release of OXT within the hypothalamic SON and PVN under basal or stimulated conditions differed between Wistar rats selectively bred for high (HAB) and low (LAB) anxiety-related behavior (1089). In this rat model of extreme differences in innate anxiety, the anxiogenic neuropeptide AVP seems to play a dominant role; it is highly expressed in HAB rats due to a SNP in the promoter of the *Avp* gene (512, 726, 1089).

Various animal studies aimed to reveal the role of *endogenous* OXT in anxiety and stress responses. This was particularly successful during periods of high activity of the endogenous OXT system, including lactation and sexual activity (755). The peripartum period is generally characterized by a reduction in emotional and physiological stress responsiveness as found in various mammals (for review, see Refs. 126, 163, 747, 951) including women (15, 246, 433, 686; for review, see Ref. 435), and this has been associated with high levels of OXT in the brain (see sect. VIIIC). However, in rats and mice, the alterations in general anxiety-related behavior peripartum were described to be controversial, with elevated anxiety levels observed in late pregnancy, and unchanged or even reduced anxiety reported in lactation, dependent on the experimental conditions and species studied (282, 419, 757, 758, 760, 1095). However, we could identify a highly consistent reduction in cued and social fear expression in lactating mice in models of cued and social fear conditioning, respectively, which was found to be strictly OXT-dependent (692a).

The brain OXT was repeatedly found to efficiently reduce anxiety, stress, and fear responses peripartum. Central infusion of an OXTR antagonist applied either icv or directly into the PVN or central amygdala, thus blocking OXTR-mediated effects, consistently elevated anxiety levels in pregnant and lactating. In contrast, a similar effect of endogenous OXT could not be revealed in virgin or male rats, indicating that OXT exerts a robust inhibitory influence on anxiety only at times of high OXT system activity (Refs. 500, 757; for review, see Refs. 755, 951).

What about males at times of high OXT activity? As described above (see sect. VIII*A*), brain OXT is also highly activated during sexual activity, as reflected by increased Fos expression in hypothalamic OXT neurons (148, 342, 829, 1112), elevated levels of OXT release within the rat PVN (1071), and the mouse lateral septum (Jurek B, Grossman C, Sommer C, Menon R, Neumann ID, unpublished observations) during successful mating. It was shown that 30 min of mating resulted in reduced anxiety-related behavior of male rats in different behavioral tests, which lasted up to 4 h (329, 1071), and in attenuated fear responses after contextual (45) and social (Grossman C, Sommer C, Menon R, Neumann ID, unpublished observations) fear conditioning in rats and mice, respectively. Infusion of an OXTR antagonist into the lateral ventricle (immediately *after* mating) prevented the observed mating-induced anxiolysis in male rats (1071), indicating an involvement of centrally released OXT.

Interestingly, in female rats, a similar effect of mating on anxiety-related behavior was only found under paced-mating conditions (773). Only during paced mating, i.e., when the female can control the speed and frequency of mating, but not during unpaced mating, there was an increased OXT release within the PVN in female rats, preventing the rise in anxiety levels as seen in female rats after non-paced mating (773).

Behavioral data from OXT knockout mice provide additional support for the importance of endogenous OXT in anxiety regulation, since female knockout mice showed greater anxiety-related behavior than their wild-type counterparts (20).

To further study the role of OXT in the regulation of anxiety, synthetic OXT has also been applied to alter the availability of OXT in distinct brain regions in various experimental settings. For instance, acute local infusion of synthetic OXT directly into the PVN, central amygdala, or prefrontal cortex resulted in a robust anxiolytic effect in both male and female rats and mice, as measured, for example, on the elevated plus-maze, elevated zero-maze, in the light-dark box, or in the four-plate test (51, 89, 747, 752, 757, 761, 896). However, only one study was able to show an acute anxiolytic effect of synthetic OXT in mice, when applied icv shortly after surgical intervention (874). So far, in most studies, the anxiolytic effect of OXT was reported regardless of sex (51, 89, 500, 752, 896). A sex-specific anxiolytic effect of OXT is mediated via a specific cluster of interneurons of the medial prefrontal cortex. These OXTR-expressing, GABAergic interneurons may release CRF

binding protein upon OXT stimulation, thus inhibiting the anxiogenic effect of CRF (616).

OXT may further interact with and facilitate the anxiolytic effects of diazepam via actions on the GABAergic system within the central amygdala (1068). This finding has important clinical implications, suggesting OXT as an add-on therapy to improve the therapeutic effects of established anxiolytic drugs such as diazepam.

The robust anxiolytic effect of OXT within the PVN was found to be dependent on the sequential activation of several OXTR-mediated intraneuronal signaling pathways. Specifically, the activation of the MAPK pathway (89, 500), as well as of TRPV channels and subsequent entry of extracellular Ca^{2+} (1044), seem to be essential for this local effect (for details, see sect. VI).

Other studies on the mechanisms underlying the anxiolytic effects of OXT, particularly within the PVN, reported that these effects are dependent on the activation of GABAa receptors by GABA (956), subsequently diminishing CRF gene transcription (131, 956). CRF is both an anxiogenic neuropeptide as well as the essential stimulator of the HPA axis, when released into the portal blood system of the pituitary stalk to activate ACTH synthesis and secretion. Thus CRF is a likely target substrate for OXT to modulate anxiety and stress responses. Indeed, acute OXT attenuated the response of hypothalamic CRF neurons by reducing stimulated *Crf* expression directly in the PVN of male rats in vivo and in vitro (499) (see sects. IV and VI).

In support of its anti-stress effect, OXT also severely attenuates the activity and responsiveness of the HPA axis, especially at times of high brain OXT system activity, such as seen in lactation. Thus central infusion of an OXTR antagonist did elevate basal ACTH and corticosterone plasma levels, and further increased the response of the HPA axis to acute stressors in virgin female and male rats (761). The same treatment potently reversed the significant attenuation of HPA axis responses in late pregnant and lactating rats, indicating that OXT—together with other brain factors activated in lactation such as prolactin (1020)—contributes to the reduced hormonal stress response in the peripartum period (757). Also in males, sexual activity and mating, associated with elevated OXT release within the hypothalamic PVN (see above; Ref. 1071), reduced the neuronal reactivity within the PVN in response to an acute stressor as indicated by lower levels of neuronal c-Fos expression (1072).

2. Effects of chronic OXT on anxiety in animal studies

Since OXT is considered a realistic treatment option, for example for anxiety and stress-related disorders, it seems of particular importance and clinical relevance to assess the effects of chronic, or intermittent repeated OXT treatment in emotionality and stress parameters. Attempts to assess the consequences of chronic OXT application in animal studies revealed differential behavioral effects dependent on the species and gender, duration and dose studied. Chronic icv infusion of OXT (10 ng/h) via implanted osmotic minipumps in ovariectomized, steroid-primed female rats over 5 days revealed an anxiolytic effect and an attenuation of the hormonal stress response of the HPA axis (1094, 1095). Similarly, an anxiolytic effect of icv chronic OXT treatment over 5 days was found in female, but not in male, HAB rats, whereas acute OXT did not alter their behavior (950). Moreover, daily subcutaneous injections of OXT over 14 days attenuated social isolation stress-induced symptoms in female voles (399). In support of a possible gender-dependent effect, chronic OXT (7 days, 20 ng/h) did not alter anxiety-related behavior in male rats (431).

In male mice, icv chronic infusion of OXT over 14 days even exerted opposite effects in a dose-dependent manner; at higher dose (10 ng/h), male mice displayed an increased level of anxiety, whereas, at lower dose (1 ng/h), anxiety-related behavior remained unchanged (815). The increase in anxiety and, in other studies, the impairment of social behaviors observed in mice and prairie voles (54, 460) after chronic icv or repeated i.n. application of OXT were accompanied by a consistent reduction in OXTR binding in several brain regions (e.g., lateral septum, amygdala, nucleus accumbens, median raphe nucleus, hippocampus) (460, 815). These studies again support the hypothesis that the abundant presence of synthetic OXT in the regional extracellular fluid results in downregulation of its receptor (see above and sect. V*F*).

When chronically infused at a lower dose (1 ng/h) during 14 days of chronic psychosocial stress (855), OXT was able to prevent some of the observed chronic stress-induced symptoms, such as hyper-anxiety, thymus atrophy, and adrenal hypertrophy in mice (815). This data conveys the option of OXT being used in the context of treatment of stress-related diseases.

Moreover, repeated icv OXT treatment facilitated wound-healing under stress conditions in Siberian hamsters, whereas repeated icv infusion of the OXTR antagonist over several days before the induction of a dermal wound delayed wound-healing possibly via dis-inhibition of the HPA axis (256).

Taken together, there is convincing evidence for the OXT system playing a powerful role in the regulation of anxiety and stress responses, and being functionally linked to the HPA axis in a reciprocal and complex manner (1017). The anxiolytic and anti-stress effects of OXT are particularly prominent during periods of activated OXT system, such as in lactation or during sexual activity.

3. OXT in anxiety and stress responses in human studies

There is also abundant evidence for OXT exerting effects on anxiety and stress responses in humans. This is not surprising given the fact that the human OXT system is responsive to stressful stimuli (see sect. IV*E*). A stress-induced increase in plasma or saliva OXT has been reported in response to physical exercise (running; Refs. 237, 439, 584) and exposure to the Trier Social Stress Test (TSST), a psychosocial stress situation consisting of public speaking and mental arithmetic in front of an audience (237, 823).

In addition, long-lasting stress effects were described to affect the reactivity of the human OXT system. Thus adult subjects having experienced a life-threatening illness in childhood or adolescence tended to have higher OXT saliva levels in response to an acute challenge (TSST), whereas mean levels of OXT did not differ between sexually abused and control subjects (824).

In husbands and wives with high, but subclinical, depressive symptomatology scores, increased OXT concentrations were found in plasma and saliva, which were at least partly mediated by higher perceived stress (452). Interestingly, in this study, warm touch intervention was able to minimize these OXT differences linked to subclinical depression.

Trait anxiety scores were found to be indirectly linked to the human OXT system activity; parallel collection of CSF and plasma samples from child and adult patients undergoing clinically indicated lumbar punctures revealed that OXT concentrations in both compartments negatively predict trait anxiety scores (159). Importantly, the authors were able to show that OXT levels in CSF and plasma samples correlated with each other, thus providing empirical support for the use of blood measures of OXT as a surrogate for central OXT activity (but see Ref. 502).

Associations between OXT concentrations in plasma or CSF, *OXTR* gene polymorphisms, and anxiety disorders have also been described, which seem to be dependent on gender and age (for review, see Ref. 755). A positive relationship between (basal) plasma OXT and state anxiety has been reported in women (452, 1013). In contrast, plasma (and CSF) OXT concentrations negatively predicted trait anxiety scores in a mixed-gender and mixed-age cohort (159), and in male subjects (1083). Similarly, high plasma OXT concentrations have been associated with reduced hormonal responses to a psychosocial stressor (996) and with lower levels of anxiety in patients with depression (913).

Moreover, associations between OXTR polymorphisms and anxiety were described with two SNPs (rs53576 and rs2254298) found to be associated with separation anxiety in depressed patients (207) and to interact with the level of anxiety symptoms in adolescent girls (1004). Similarly, in a large study assessing multiple *OXTR* SNPs, a link between *OXTR* genotype and depression, anxiety, and stress scores as well as retrospectively assessed early life stress exposure was found (732). However, the physiological consequences of *OXTR* polymorphisms for the functioning of the OXT system remain unknown (see sect. XII).

The existing data from animal and human studies suggest that stressful events activate both peripheral and central OXT release (see **TABLE 3**). This is an important observation with implications for human studies, since it speaks in favor of peripheral OXT measures being a potential biomarker of the general reactivity of the endogenous, including the intracerebral OXT system under the condition of defined stimulation or of impaired OXT signaling linked to psychopathologies (159). However, several limitations have to be considered in this context (see sect. XIII; Ref. 753). Recently, the Regensburg Oxytocin Challenge (ROC) Study has been published, which included saliva sampling both under basal conditions and in response to well-defined stressful activities, such as running and sexual activity (237). Both running as well as sexual self-stimulation induced a rapid 2.5-fold increase in salivary OXT after 10–15 min, with similar levels found in men and women. Moreover, a profound increase in salivary OXT was also found in response to exposure to psychosocial stress, as induced by the TSST. In contrast, breastfeeding did not result in any measureable increase in salivary OXT; it is possible that the short pulses of OXT secretion that are characteristic for lactation were simply missed during the sampling procedure. Taken together, the ROC test might provide a useful paradigm for humans to assess the ability of the body's OXT system to respond to defined physiological challenges as a biomarker (237).

Taken together, the activity of the endogenous OXT system, including basal and stress-induced neuronal OXT synthesis, intracerebral and peripheral OXT release, OXTR expression and binding, might essentially predict an individual's trait anxiety and fear responsiveness (753). Genetic, epigenetic, or physiological (see below) factors may influence this balanced activity to the right or left side of an emotionality continuum contributing to individual differences in anxiety and stress responses **(FIGURE 11)**.

However, despite the profound anxiolytic effect of OXT shown in rodents, only a few studies assessed the potential anxiolytic properties of i.n. OXT in patients with general anxiety disorders (652, 755). Only a slight but beneficial effect of daily OXT administration over 3 wk could be shown in male anxiety patients (320).

With respect to OXT effects on general anxiety, it has also been shown that the positive correlation between higher trait anxiety in male students and their poor perceptions of

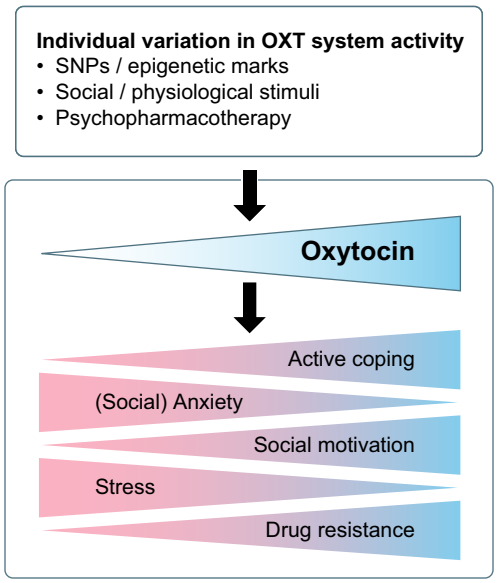


FIGURE 11. Hypothetical model depicting the *1*) influence of genetic and epigenetic factors, social and physiological stimuli, and psychopharmacotherapy (e.g., i.n. OXT) on the activity of the brain OXT system and availability of OXT in the brain [from low (*left*) to high (*right*)], and *2*) its implications for behavioral regulation from mental health to psychopathology.

speech performance in a naturalistic social stress task, which was found in placebo-treated students, disappeared after i.n. OXT (19). These results indicate that synthetic OXT may reduce negative cognitive self-appraisals and attenuates negative cognitive responses to stress in anxious individuals.

In a study differentiating predictable and unpredictable fear and anxiety responses, respectively, i.n. OXT was found to increase anxiety. Specifically, defensive stress responses, i.e., startle responses to unpredictable, but not to predictable, threat (shock) were elevated by OXT (396). The authors discussed the interesting hypothesis that this effect of OXT to enhance defensive responses to uncertain contexts is in line with the observation that OXT boosts defensive, partly aggressive behaviors toward unfamiliar individuals (235), which may trigger unpredictable social situations.

A possible reason for the few reports on general anxiety after OXT treatment in humans is the fact that i.n. OXT seems to be rather effective for the treatment of symptoms of social fear in patients suffering from social anxiety disorders rather than for general anxiety disorder. Thus an overwhelming and still rising number of studies reports on i.n. OXT effects on various, sometimes only slightly differing aspects of social behavior and responsiveness to social stress-related stimuli in healthy subjects and social anxiety patients. Here, a few examples can only be explained, and the reader is referred to detailed reviews elsewhere (465, 652, 694, 755).

Several recent studies described a social stress-buffering effect of i.n. OXT in healthy humans. For example, i.n. OXT reduced anxiety levels, increased calmness, and lowered the skin conductance level throughout the test in healthy men, who were exposed to the TSST (242, 432). Importantly, the antistress effects of OXT were particularly prominent, when men received social support by a best friend (432). The same effect of OXT on cortisol responses to public speaking was found in individuals with impaired emotional responsiveness (850). Another study showed that i.n. OXT improved communication behavior in both men and women during a couple conflict and reduced plasma cortisol levels during the conflict (269).

Importantly, i.n. OXT was found to reduce social anxiety symptoms in patients with social anxiety disorder (for review, see Refs. 652, 755). In one study, i.n. OXT was applied as an adjunct to exposure therapy, and it was found that OXT improved the positive evaluation of appearance and speech performance. However, OXT did not affect symptom reduction, dysfunctional cognition, or life-impairment measures, but rather improved mental representations of self following exposure therapy (404). In fragile X patients, who also display symptoms of social anxiety, i.n. OXT improved eye gazing and reduced cortisol response to a social challenge (412).

Kirsch et al. (537) were the first using functional magnetic resonance imaging (fMRI) to show that i.n. OXT potently reduced the neuronal activation of the amygdala in response to non-social or social fear-inducing visual stimuli (537). Furthermore, i.n. OXT reduced the coupling of the amygdala to brain stem regions implicated in autonomic and behavioral manifestations of fear. The reduction in amygdala activation by i.n. OXT was more pronounced when volunteers were exposed to threatening social stimuli (fearful faces) than to non-social scenes (537). These data are in line with several subsequent reports on inhibitory OXT effects on amygdala responses to facial expression, which were found to be independent of the emotional valence, i.e., OXT reduced neuronal amygdala reactivity to happy, angry, or fearful faces in men (276, 506; for review, see Refs. 694, 755). Another study compared i.n. OXT effects in patients with general anxiety disorder in comparison with healthy controls. They described that OXT attenuated the heightened amygdala reactivity to fearful faces in anxiety patients only, whereas it had no effect on neuronal activity in healthy controls (576).

OXT applied i.n. also modulated the amygdala-prefrontal connectivity, a neural circuit known for social threat processing and emotion regulation and found to be aberrant in patients with social anxiety disorder. Specifically, i.n. OXT "normalized" the neuronal activity within this circuitry under resting-state conditions and in response to fearful faces in social anxiety disorder patients (273, 388). The effects of

i.n. OXT on amygdala reactivity seemed to be gender-dependent, since, in contrast to men, enhanced neuronal activation was found in the left amygdala and other regions in response to scenes depicting social (fearful) faces as well as non-social threatening stimuli following i.n. OXT treatment in women (277, 623). It was concluded that in females OXT might promote the detection of threatening stimuli in the environment (623) **(FIGURE 12)**.

4. OXTR-mediated regulation of fear in animal studies

Several psychiatric disorders such as PTSD, social anxiety disorders (SAD), and panic disorder are characterized by the inability to extinguish fear memories. In the context of OXTR-mediated effects, it appears to be important to distinguish between non-social and social causes of trauma. Therefore, to reveal the underlying neurobiological mechanisms, and the involvement of OXT in fear extinction, animal models of cued and context fear conditioning (mimicking general fear and PTSD) (149, 788, 851, 943) and of social fear conditioning (mimicking social fear and social trauma) (1023) have been established (for review, see Refs. 755, 1022).

A) OXTR-MEDIATED EFFECTS ON CUED AND CONTEXT FEAR. With respect to non-social fear, it has been shown that OXT neurons are activated following fear acquisition and fear extinction, implicating a role for the endogenous OXT system (1144). However, the effects of OXT on cued or context fear expression and extinction seem to depend strongly on the sex, species, timing and brain region studied, and the doses of OXT or its agonists used. For example, in male Wistar rats, icv OXT infused before *cued fear acquisition* did not affect cued fear conditioning and learning of the association between the conditioned and unconditioned stimulus, but reduced cued fear expression and accelerated fear extinction 24 h later (1023). In support, infusion of OXT or its agonists at relatively low doses (between 3 ng/0.3 μl and 75 ng/0.3 μl) into the central or basolateral amygdala of Wistar rats before context conditioning even impaired fear acquisition and reduced fear expression (freezing) on the next day, suggesting weaker encoding of the context-shock association (150).

In contrast, icv OXT infusion before *cued fear extinction* training even impaired fear extinction in both rats and mice (1023). This is in line with the observation in Wistar rats of enhanced expression of context fear by infusion of synthetic OXT or the selective OXT receptor agonist, TGOT, into the central amygdala of Wistar rats *before fear extinction* (150).

In contrast to these results, another study reported that OXT infusion bilaterally into the central amygdala of female Wistar rats before context fear extinction decreased freezing responses in fear-conditioned rats without affecting cardiovascular fear response. The authors hypothesized that OXT signaling as part of an inhibitory network within the amygdala (462) can modulate the central amygdala out-

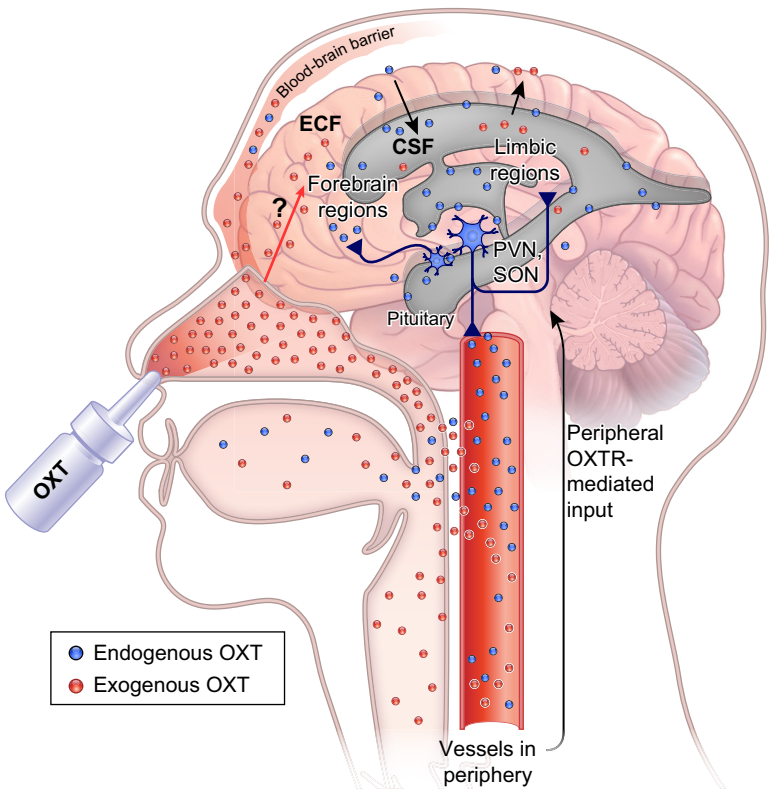


FIGURE 12. The brain OXT system: projections, release, neuronal OXTR-mediated input from the periphery, and external application. ECF, extracellular fluid; CSF, cerebrospinal fluid; PVN, paraventricular nucleus of the hypothalamus; SON, supraoptic nucleus; AN, accessory nuclei.

puts through separate neuronal circuits, thereby individually steering behavioral and physiological aspects of the fear response (1067). Confirming these findings, optogenetic stimulation of OXT neurons within the PVN before fear extinction resulting in the local release of endogenous OXT within the rat central amygdala also reduced cued fear expression (544, 1067). Specifically, OXT was found to modulate excitatory inputs from the basolateral amygdala and cerebral cortex, thereby affecting distinct neuronal populations in the central amygdala, the major output region of the amygdaloid complex (462, 597). The inhibition of central amygdala outputs by OXT was described to be realized through separate neuronal circuits, allowing separate reduction of, for example, freezing responses or cardiovascular responses in fear-conditioned rats (1067). In line with these results, pre-extinction infusion of OXT directly into the basolateral amygdala also suppressed context fear in an OXTR-dependent way (150).

Partly contrasting and brain region-dependent effects were found when synthetic OXT, or the OXTR agonists TGOT or WAY-267464, were infused in higher doses into male Sprague-Dawley rats (544, 579). For example, infusion of the OXT agonist WAY-267464 or TGOT, but not of OXT, into the central amygdala before fear conditioning reduced context fear expression, whereas OXT infusion enhanced freezing and impaired extinction when infused into the basolateral amygdala. When OXT was infused before fear extinction, impaired extinction was reported after infusions into the basolateral amygdala, but not central amygdala, of male rats; infused into the infralimbic medial prefrontal cortex before extinction, OXT or WAY-267464 facilitated fear extinction (579).

In summary, these partly controversial findings imply a critical role for OXT signaling in amygdala-based regulation of aversive learning. OXT may inhibit but also enhance context and cued fear expression and extinction dependent on *1*) the site of action within amygdalar subregions, *2*) the doses used, *3*) the precise time point of application of OXT or its agonists, *4*) the precise quality of fear, and *5*) sex, species, and strain studied. Thus increasing local OXT neurotransmission during traumatic events may prevent the formation of aversive memories, whereas, in contrast, OXT treatment before fear extinction training cannot be excluded to even delay and impair cued or context fear extinction. Since treatment before extinction training would be the comparable time point for psychotherapy in PTSD patients, caution is needed before recommending OXT for the add-on treatment of PTSD, especially in case the trauma is of non-social nature (see below).

B) OXTR-MEDIATED EFFECTS ON SOCIAL FEAR. Social anxiety and social phobia are major symptoms of social anxiety disorder (SAD) and PTSD, and characteristic for various other psychopathologies, such as major depression or autism (523, 1022). SAD is characterized by the persistent fear and avoidance of social situations. In line with its profound prosocial effects, brain OXT was found to be essential for naturally occurring social preference behavior in rats and mice (648): When intracerebral OXTR were blocked, male rats and mice avoid unknown conspecifics, which they would otherwise prefer to explore with high interest. Moreover, icv infusion of OXT reversed social avoidance and rescued social preference behavior in male rats after they were socially defeated by a slightly larger, aggressive conspecific resident (648). These findings support the hypothesis that brain OXT generally contributes to naturally occurring social preference and social competence. It is of interest to note that OXT knockout mice display normal social preference behavior, indicating other factors contributing to this essential behavioral phenotype and replacing OXT functions (210).

In support of a role of OXT in social defeat stress-induced social fear, it was shown that adeno-associated virus-induced OXTR knockdown and OXTR overexpression within the lateral septum reduced and enhanced freezing responses, respectively (410). Furthermore, social stress-induced conditioned freezing was prevented by infusion of an OXTR antagonist into the lateral septum, whereas infusions of synthetic OXT were without effect (410).

To model social phobia specifically and to study OXT involvement in social fear, a mouse model of social fear conditioning has been established (1024). In this social fear conditioning paradigm, mice receive a mild electric footshock, when actively investigating a conspecific during social fear acquisition, resulting in robust social fear 24 h later. The brain OXT system showed distinct alterations in socially fear-conditioned mice. First, an elevated OXTR binding was found in regions associated with the fear circuitry (dorsolateral septum, central amygdala, hippocampus, median raphe nucleus), which was reversed after social fear extinction (1023). The second consequence of social fear conditioning was an attenuated release of OXT within the lateral septum during social interactions, which was, in contrast, strongly stimulated in non-conditioned mice during social exploration (1148). Thus lack of availability of OXT in the local extracellular fluid may at least partly be responsible for increased OXTR expression and social fear (see sect. V*D* and Ref. 815).

Similarly, an increased OXTR expression has been described in the lateral septum of chronically defeated mice (624), and a virus-induced overexpression of the OXTR within the lateral septum has been associated with increased social stress-induced fear expression (see above; Ref. 410). These results indicate a specific role of OXT in the lateral septum in social fear and suggest a social fear- or social stress-induced reduction in the availability of the OXTR ligand, i.e., by reduced local OXT release. Consequently,

increasing local OXT concentration by intraseptal (but also icv) OXT infusion before social fear extinction training strongly abolished fear expression and reinstated social preference behavior in male mice (1148). In support, physiological conditions associated with high activity of the brain OXT system, such as lactation and sexual activity, have recently been linked to lower social fear expression, with endogenous OXT being strongly involved in these behavioral alterations (692a).

The consistent findings on a prominent involvement of the brain OXT system in social fear and the efficient effects of synthetic OXT to reverse or prevent social fear substantiate the assumption that the brain OXT system is of particular importance for the etiology of social fear-related disorders and may become a realistic treatment option for SAD.

5. OXT regulation of non-social and social fear in human studies

In addition to i.n. OXT effects on acute anxiety and stress responses (see sect. VIII*F*), OXT was also tested in the context of fear conditioning in humans. In a Pavlovian fear conditioning/extinction paradigm, i.n. OXT was administered to healthy men before *non-social* fear conditioning and was found to strengthen the conditioning effect, since faster behavioral and neuronal (fMRI) responses to the conditioned stimuli were seen (301). This indicates that OXT increased the learning performance during fear acquisition and is in line with the observation that i.n. OXT increased the startle response to unpredictable shocks (396).

However, when OXT was applied after conditioning, i.e., 45 min before fear extinction training, an increase in fear-potentiated startle responses was found during the early stage of extinction training but a facilitated fear extinction recall on the next day (6). Similarly, at the same time point before extinction training, OXT increased electrodermal responses along with prefrontal cortex signals to conditioned fear found in the early phase of extinction, but a more rapid decline of skin conductance responses was detected in the late phase of extinction (300). It is interesting to note that i.n. OXT did not affect amygdala functions in the context of fear conditioning responses, suggesting that the observed behavioral and psychophysiological effects result from activity changes in extra-amygdalar regions (301).

In the context of *social fear*, an important association between epigenetic markers of the endogenous OXT system and the symptoms of SAD has been reported. Thus reduced OXTR methylation in blood cells of patients with SAD was associated with the severity of the disease, stress-induced cortisol responses, and increased amygdala activity (1145). Decreased methylation is possibly indicative of increased OXTR expression. Although there is still uncertainty to which extent epigenetic markers of blood cells predict unidirectional alterations in neurons, these data support the finding of elevated OXTR expression in various brain regions in socially fear-conditioned mice (1148).

The first study on effects of OXT and social fear involved Vietnam veterans with PTSD (826). However, no beneficial effects of OXT on physiological responses to combat imagery were observed. A variety of subsequent studies demonstrated the ability of OXT treatment to attenuate social stress and fear conditioning responses. For example, it was shown that OXT attenuated and partly reversed the negative (verbal) evaluation and likability rating of faces, which have been aversively conditioned by co-administration of an electric shock to the healthy test person (819). Although mood ratings remained unchanged, i.n. OXT also prevented the rise in neuronal activity in the extended/dorsal amygdala, fusiform gyrus, and other regions relevant for fear conditioning as assessed by fMRI (819). These data provide direct support for the effects of OXT on social fear as seen in socially fear-conditioned mice (1148).

Taken together, in the context of fear conditioning and PTSD, the time point of OXT application as well as the context (social vs. non-social) have to be carefully considered before i.n. OXT can be used as a safe treatment option for traumatized patients. Specifically, the data from human studies, which partly support data from rodents, suggest that OXT may promote fear learning by a rapid and flexible adaptation to non-social fear signals but may also delay and impair fear extinction processes, especially extinction of non-social fear. Thus, in response to non-social fear signals, OXT may even elevate the vulnerability for a pathological manifestation of the trauma. In contrast, in a social context, beneficial effects of OXT have consistently been shown in animal and human studies, indicating that OXT may become a realistic treatment option for social anxiety disorders and social trauma emphasizing its translational potential.

F. Regulation of Depression-Related Behavior

1. OXT and depression-related behavior in animal studies

Given that half of the patients diagnosed with major depression disorders (MDD) meet criteria for co-morbid anxiety disorder (521) and that MDD is accompanied by severe social dysfunctions, which include social withdrawal, social fear, impaired social recognition, or aggression, it is reasonable to assume that OXT has a potential role in the pathophysiology of MDD. Thus the anxiolytic and pro-social effects of OXT described above also in humans may be of therapeutic benefit in these patients (for review, see Ref. 950). Moreover, there is accumulating evidence for an involvement of OXT also in the regulation of depression-like behaviors, such as passive vs. active stress coping style, escape behavior, or anhedonia, which is summarized below.

Various results arriving from animal studies suggest a significant role of OXT in depression-related behaviors, as shown in tests assessing passive vs. active stress coping strategies, such as the forced swim test in rats, mice, and voles (216, 297, 948), or the tail suspension test in mice and voles (103, 949, 970). In these tests, passive coping behavior is interpreted as depression-related behavior. Also, escape behavior in the learned helpless test is taken as indicative of depression-like behavior (215). Since anhedonia is a core symptom of MDD, tests for anhedonia such as the sugar preference test are also employed.

Thus it was demonstrated that OXT, applied repeatedly intraperitoneally (ip) over 10 days in mice decreased the immobility time in the forced swim test (35). The same effect was replicated after acute ip injection in the tail suspension test in aged rats and mice (34, 875). Similarly, subcutaneous OXT decreased the number of escape failures in the learned helpless test (771), indicative of an antidepressant-like effect (215). However, we have to keep in mind that peripherally applied OXT has only limited access to the brain compartment, even when applied in supraphysiological amounts. Therefore, it seems important that antidepressant-like effects of OXT were also shown after icv administration in the tail suspension test performed shortly after surgery (875). However, in this study, administration of the small-molecule OXTR agonist WAY-267464 failed to induce an anti-depressant effect, even at supraphysiological doses.

Similarly, in a psychopathological rat model of anxiety, i.e., HAB rats, which display a strong depression-like phenotype, we failed to demonstrate an anti-depressive effect in the forced swim test after either acute or chronic icv OXT infusion (950). In addition, the activity of the brain OXT system (expression of OXT or OXTR, OXT release) was not detectably altered in HAB rats (1089).

With respect to the endogenous OXT system, exposure to various stressors, including forced swimming, stimulates the release of OXT within the central amygdala and the PVN (see sect. IV) in rats. This again suggests a link between OXT and stress coping. However, local administration of an OXTR-A revealed that OXT release within the central amygdala during forced swimming is rather linked to a more passive stress-coping style in male rats (297).

However, within the PVN, locally released OXT has been shown to attenuate stress-induced hypothalamic CRF neuronal activity (131, 499, 768, 956), with CRF being a potent promoter of depression-like, i.e., passive behavior (512). Since central OXT actions have also been linked to the promotion of sleep shown in male rats (582), the possibility exists that brain OXT contributes to a generally reduced arousal and physical activity, which is difficult to distinguish from possible anti-depressive effects. Antidepressive and sedative effects might be strictly brain region-specific. In general, from few animal studies, the existing evidence for the role of the endogenous OXT system in active vs. passive stress coping, interpreted as depression-like behavior, is rather inconclusive.

In a model of pair separation-induced depression-like behavior in monogamous prairie voles (*Microtus ochrogaster*; Refs. 103, 981), partner loss compromised the brain OXT system (100). Separation from the female partner reduced OXT synthesis in the PVN as well as OXT release and OXTR density in the nucleus accumbens shell. Further evidence for brain OXT being involved in depression-related behavior in bonded prairie voles after separation is given by the fact that local pharmacological blockade or knockdown of OXTR using short hairpin RNA (shRNA) targeting the prairie vole OXTR within the nucleus accumbens shell increased their passive stress-coping. In contrast, local infusion of OXT prevented passive stress coping after separation. Interactions of the CRF receptor CRFR2 and the OXT system were hypothesized to maintain the balance between active and passive stress-coping in response to social stimuli and to mediate the emotional consequences of partner loss (100).

2. OXT and depression in humans

Several clinical studies aimed to correlate plasma OXT concentrations with depressive symptomology. Some studies found reduced plasma OXT concentrations in patients suffering from major depressive disorder (MDD) compared with controls in male (352, 1130) and female (794) patients. However, after successful antidepressive treatment (SSRI or tricyclic antidepressants) as measured by the Hamilton Depression Rating Scale, there was no change in plasma OXT in relatively small cohorts of patients.

OXT has also been studied in relation to electroconvulsive therapy (ECT), which is one of the most effective treatments for severe MDD, with a relatively rapid effectiveness. Although an ECT-stimulated increase in plasma OXT has been repeatedly shown (257, 959), a clear relationship between ECT, plasma OXT, and clinical outcome could not be confirmed (258, 958). Thus the acute rise in plasma OXT in response to the stressful ECT is likely to reflect a stress-induced event.

Other studies could not find any differences in plasma OXT between MDD patients and healthy controls (511; see also Ref. 891) but found a larger variation within the MDD group (218, 1047). The larger variation of OXT levels in MDD patients is likely due to correlations of plasma OXT with the severity of various symptom clusters in MDD. Thus a positive correlation was found, for example, between plasma OXT and *1*) severity of MDD symptoms as assessed during an affiliation-associated imagery session (218), *2*) impulsiveness and negative emotionality (73), and

3) reward dependency and novelty seeking, as assessed in a temperament and character inventory (70).

A negative correlation between OXT and depression- and anxiety-symptom severity in depressed patients has also been reported (913). As one study reported, gender-specific plasma OXT levels and responsiveness may explain some of the contradicting results of previous reports. In more detail, depressed women exhibited lower mean OXT concentrations than depressed males and healthy female controls. However, depressed men exhibited a trend toward increased plasma OXT levels compared with controls (1126). A brain gene expression profiling study, using RNA-sequencing with samples from healthy controls, untreated suicidal MDD and sudden death, non-suicidal MDD patients, revealed lower expression of genes involved in oligodendrocyte differentiation, regulation of glutamatergic neurotransmission, and OXTR expression in both groups, suicide and depression, independent of sex (798).

However, in general, plasma OXT of MDD patients assessed under basal conditions rather seems inconclusive and is certainly not a reliable biomarker of MDD.

A number of studies has also assessed OXT concentrations in the CSF of MDD patients. Quantification of OXT in the CSF seems generally to be a more promising way to assess the link to a given behavioral phenotype, since it integrates processes of intracerebral release, central diffusion, and degradation of OXT within the brain. However, either no difference in OXT concentrations in CSF between MDD and control subjects (253) or only a trend toward lower OXT concentrations in a small number of MDD patients, who were further characterized as dexamethasone suppressors (827), was found.

Several postmortem studies assessed the number of hypothalamic OXT neurons and OXT mRNA levels, which consistently suggested an increased activity of the OXT system in MDD. Thus the number of OXT-immunoreactive neurons in the PVN was increased in tissue samples of both MDD and bipolar patients compared with controls (846). Also, increased OXT mRNA levels were found in the PVN, but not SON, of melancholic MDD patients compared with non-melancholic subjects using in situ hybridization (696). In line with this, a trend toward increased OXT mRNA levels in the PVN of the MDD group compared with age-matched controls was found by quantitative PCR in snap-frozen brain tissue after dissection of the SON and PVN by laser capture microscopy (1077). The increased activity of OXT neurons in MDD has been hypothesized to be linked to the eating disorders in depression (983).

Similar to the effects of antidepressive drugs such as selective serotonin reuptake inhibitors (SSRI) (421, 422, 769), several human studies have revealed a positive effect of i.n. OXT on the processing of both positive and negative facial cues as well as decreasing amygdala activity to fearful faces as described above (267, 276–278, 537). Thus i.n. OXT may reduce the salience of threatening social cues. Together with the general demonstration of robust pro-social effects of OXT, these data implicate that OXT may be useful as an adjunctive agent in MDD patients, especially in those with high ratings in social dysfunctions and social phobia.

OXT has also been studied in the context of postpartum depression. Thus women who received intravenous OXT during delivery to promote labor and to accelerate the birth process were tested for postpartum depression disorder within the first year postpartum. Surprisingly, women with or without a history of depressive disorders had a higher relative risk of developing MDD or an anxiety disorder when they have been treated with OXT during delivery compared with women who were not exposed to OXT (564). To which extent this is related to possible complications around birth making OXT treatment necessary remains to be shown.

In a recent study on a cohort of mothers and their offspring, children of depressed mothers showed low baseline urine OXT levels and attenuated OXT response interaction. When maternal OXT levels were low, the OXT response of the child was negatively affected by maternal depression. However, when maternal OXT levels were high, child OXT was unaffected, suggesting that maternal OXT functionality buffers the effects of depression on the child (840).

Taken together, the evidence from animal and clinical studies suggests a potential role of the OXT system in the pathophysiology of MDD. This, however, is neither consistently reflected by increased plasma or CSF OXT concentrations, nor by treatment effects. Nevertheless, there is a potential therapeutic benefit of OXT in at least some subsets of MDD patients and on some symptoms accompanying MDD. Its significant involvement in aspects of behavioral and neuroendocrine regulation, including its anxiolytic and antistress effects, the promotion of various social behaviors and of social reward, make the brain OXT system a promising candidate central to possible add-on therapeutics. Furthermore, OXT interacts with various classical neurotransmitter and neuropeptide systems central to MDD, such as the serotonin, noradrenaline, dopamine, and the CRF systems (see sect. IV*F5*).

IX. LEARNING AND MEMORY

Learning and memory involve acquisition and the preservation of new environmental information based on neuronal plasticity within specific brain circuitries (1052). An adequate behavioral response to defined environmental stimuli, both social and non-social, can only be displayed when new and relatively stable patterns of interneuronal commu-

nication are generated at cellular levels. Various aspects of OXT affecting learning or memory processes have already been touched above, e.g., in the context of social bonding (mother-infant bonding, pair-bonding) or fear conditioning, which require the storage of information regarding a conspecific or a context. In this section, we will specifically focus on the involvement of brain OXT on non-social (active and passive avoidance, spatial memory, object memory) and social (juvenile recognition) learning, as revealed by numerous animal studies, as well as on non-social vs. social memory effects of i.n. OXT in humans.

A. OXT and Non-Social Memory in Animals

One of the first behavioral effects of OXT (and AVP) observed was that on memory retention in rats (248). Thus icv administration of synthetic OXT after a learning session attenuated passive avoidance responses induced by an electric shock. In addition, icv OXT increased the extinction of (active) pole-jumping avoidance behavior (466). Accordingly, brain OXT was first considered an amnesic neuropeptide, supported by the finding that an OXT antiserum, in contrast to an AVP antiserum (1051), facilitated memory processes (Ref. 248; for review, see Ref. 560). However, site-specific effects (dorsal septum vs. hippocampal dentate gyrus, raphe nucleus) on passive avoidance memory contradicted the assumption that OXT may act as a general amnestic peptide in this behavioral test (Ref. 555; for review, see Ref. 314).

As mentioned above (see sect. VIII*D*), OXT was described to act at the OXTR within the dorsal hippocampus to improve spatial memory during lactation (1011). This memory effect of OXT was shown to be due to the facilitation of long-lasting, long-term potentiation at the synapses from Schaffer collateral fibers onto CA1 pyramidal cells in hippocampal slices (1011). Since icv OXT also improved long-term spatial memory in virgin mice, it was concluded that the effects of OXT on synaptic plasticity and spatial memory are more general and not restricted to the peripartum period when the brain OXT system is generally active. In support of this assumption, chronic icv OXT infusion over 7 days slightly improved object recognition in male rats (431). However, the general memory-enhancing effect of brain OXT was challenged by the finding that OXT knockout mice showed an unchanged spatial memory performance in the Morris-Water-Maze and the Y-Maze (328). In line, object recognition as assessed in the object discrimination test was not affected by icv OXTR antagonist in male mice (649), indicating that brain OXT may rather play a minor role in learning and memory functions associated with the processing and storage of non-social information.

B. OXT and Social Memory in Animals

Consistent effects of OXT on memory processes were found in a social context, both in laboratory animals and in humans. In rodents, social memory can be tested, for example, in social recognition (228) and the social discrimination (313) tests. In the social recognition test, repeated exposure to a conspecific animal (juvenile or ovariectomized female) should result in a declined interest to investigate it, reflecting social memory. In the social discrimination test, simultaneous exposure of the known and a novel conspecific leads to increased investigation toward the novel one, reflecting social discrimination abilities and social memory.

OXT infused into the cerebral ventricles of male rats enhanced social memory, but only at low doses (74, 832), whereas it may interfere with social memory at high doses (228, 831). Region-specific effects were found in the lateral septum and the medial preoptic area, where OXT improved juvenile recognition abilities in adult male rats (833).

In support of a role of endogenous OXT in social discrimination abilities, OXT was found to be released in the lateral septum in male mice during social interaction and investigation of adult male conspecifics (1148), and in male rats during retrieval, but not during the acquisition or maintenance, of social memory in the social discrimination test (649). Infusion (icv) of an OXTR antagonist and blockade of OXTR immediately after acquisition of social memory impaired the maintenance of social memory and social discrimination abilities in both rats and mice (649). However, the impact of the social stimulus seems important for social memory abilities; male rats recognized a previously encountered male juvenile for only 60 min, whereas social recognition of a female adult rat lasted for 120 min. OXT actions within the lateral septum were found to mediate both juvenile and female recognition, whereas, within the medial amygdala, OXT facilitated memory for adult females only (649).

Another region where OXT may promote olfactory coding and, subsequently, social memory is the olfactory bulb, which contains few OXT fibers and OXTR (777, 1040). Bilateral OXT infusion into the olfactory bulb prolonged the memory performance in the social discrimination paradigm in male rats. Although a local OXTR antagonist by itself did not alter social memory (271), it blocked the local effects of OXT, demonstrating a specific, OXTR-mediated mechanism within the olfactory bulb (270). Moreover, the olfactory bulb norepinephrine system was found to be activated by local OXT, and the resulting activation of alpha-adrenoreceptor seems important for the memory-enhancing effect of OXT within that region (270), as for memory and recognition responses in general (395, 501, 525).

Oettl and coworkers (777) described that OXT promotes olfactory coding already at the level of the anterior olfactory nucleus, the most anterior portion of the olfactory cortex, which is among the brain regions with highest OXTR expression (358, 1028, 1040, 1117; see **TABLE 2**)

and receives dense innervation from OXT neurons of the PVN (544). Local OXT actions are required for olfactory information processing and social memory in female rats and male mice, since deletion of OXTR within the anterior olfactory nucleus impaired social recognition in female rats. These local effects are likely due to glutamate-mediated top-down effects on glomerular cells in the main olfactory bulb.

An involvement of endogenous OXT in female social memory formation was also found after icv infusion of an OXTR antagonist, which interfered with the ability to establish short-term olfactory memory (311). However, in contrast to male rats, icv administration of synthetic OXT did not alter social memory formation in female rats.

In female mice, the medial amygdala has been identified as a possible site of action of OXT to promote social memory, as shown by local infusion of antisense oligonucleotides targeting OXTR expression in a locally and spatially specific way, which resulted in impaired social memory abilities (185). Interestingly, these antisense-treated mice also showed an initial increase in risk-assessment behavior, supporting the role of OXT in attenuating social fear. In proestrus females, interindividual differences in social recognition abilities were related to the differential expression of OXT and AVP, ERα and ERβ specifically within the medial preoptic area. In contrast, the initial social motivation for investigation correlated with the expression of estrogen, progesterone, and OXTR in the dorsolateral septum, suggesting that these receptors may modulate social interest without affecting social recognition (194).

Activation of the endogenous OXT system as seen peripartum seems to boost special aspects of memory formation in females. In addition to improved spatial memory, as found in mice (1011; see above), OXT released within the olfactory bulb peripartum facilitates social recognition of a ewe for her lambs (516, 524; see sect. VIIIC). In support, optogenetic stimulation of PVN OXT neurons triggering intracerebral release of OXT prolonged social investigation and, subsequently, improved social recognition in virgin female rats (777).

The importance of the brain OXT system for social memory processes was further demonstrated in male OXT knockout (328) and OXTR knockout (991) mice. These knockout mice showed an impaired ability to recognize a female ovariectomized mouse used as social stimulus. Acute infusion of OXT either icv or directly into the medial amygdala before memory acquisition (and social investigation) rescued social memory in OXT knockout mice (327, 328), indicating that locally released OXT and subsequent OXTR-mediated signaling are both necessary and sufficient for social recognition in the mouse. Similar deficits in social memory were also described in female OXT knockout mice (328).

In a conditional OXTR knockout mouse line (601), where OXTR expression was prevented specifically within the forebrain, resulting in OXTR reduction in the lateral septum, hippocampus, and ventral pallidum, but not in the amygdala, impaired social memory of male mice for familiar females was reported (601).

Indirect support for a role of OXT in social learning and memory abilities arrived from an above-mentioned study using CD38$^{-/-}$ mice, with CD38 being an essential transmembrane glycoprotein for neuronal OXT release (489; sect. IV*D*). These mice, in which low OXT plasma concentrations were found, failed to recognize familiar conspecifics; however, to which extent the lack of CD38 indeed affects intracerebral OXT release has not been shown (749).

In addition to rodents, OXT motivates social memory functions also in monkeys. Acute, aerosolized OXT improved working memory (i.e., the ability to briefly hold and process information) and gaze-following (i.e., tracking the direction of others' gazes) in infant macaque monkeys (*Macaca mulatta*), but only in males (939). These unexpected sex differences may be due to interactions with gonadal steroids and indicate possible sex-dependent effects of OXT on learning and memory.

Overall, these results show that brain OXT is an essential factor specifically for social memory in male and female mammals that, depending on the biological relevance of the social stimulus, acts within distinct brain regions such as the lateral septum, amygdala, and olfactory bulb to improve social discrimination abilities.

C. OXT and Memory in Humans

A number of studies have reported an impact of OXT applied via the nasal route on human cognitive and memory functions using an identical placebo treatment containing all ingredients except active OXT for control. In most cases, either a within- or between-subject design has been applied. These studies convincingly demonstrate that the context of information to be recognized or stored significantly matters. Thus there are numerous studies on the differential effects of i.n. OXT on long-term memory of either non-emotional stimuli (e.g., non-emotional words, objects, neutral faces) or emotional stimuli (e.g., emotional words, faces, pictures), which have extensively been reviewed by Brambilla et al. (110). In addition, differential effects of OXT were found on the storage of social vs. non-social information (for review, see Ref. 405).

In the context of long-term, *non-emotional* information storage and retrieval, a general impairment has been de-

scribed independent of the precise time point of i.n. OXT-treatment. For example, the first study reported that the ability to recall neutral word pairs after learning and in later recall decreased in men treated with 15 IU of OXT (331). Similarly, OXT (10 IU) administered during the memory-retrieval phase, but not before the encoding phase, decreased memory performance (318). OXT (20 and 24 IU, respectively) was also found to reduce the number of correctly remembered words after the initial presentation and impaired the efficacy of storage, when administered before learning a word-list (125). These effects were found irrespective of the meaning of the words (434) and of non-social vs. social stimuli [i.e., houses vs. faces (438)].

There are also studies reporting a temporary impairment of verbal episodic memory in women during pregnancy and postpartum (117), and it has been concluded that OXT may have an important biological function by inhibiting acquisition of aversive experiences during labor (434).

Only a few studies reported a positive effect of i.n. OXT administration on non-emotional face recognition. For example, acute i.n. OXT improved face recognition in a very specific context, i.e., when faces of people from another race (black) compared with same race faces (white) had to be recognized by participants of Caucasian ethnicity (86). When OXT was administered before the encoding phase, it increased the percentage of correct responses to previously seen faces of other race members.

Moreover, patients with schizophrenia reported a beneficial effect on long-term verbal memory for non-emotional stimuli after 3 wk of daily i.n. OXT administration (319).

In contrast to non-emotional information processing, several recent studies reported rather positive, but also partly contrasting, effects of i.n. OXT on long-term memory of specific emotional stimuli (e.g., faces with emotional expressions of anger, happiness or fear, aversive pictures, emotional words) (for review, see Ref. 110). For example, OXT enhanced the accuracy in a recognition memory task and familiarity ratings for happy faces, but not for neutral or angry faces, in adult men (403). In contrast, others found improved identity recognition selectively for faces with a neutral or angry expression, but not for happy faces after i.n. OXT (911). In line with OXT-promoting information storage and processing with emotional value, such a promnestic effect of OXT was also found for the memory recall of emotional *words* with positive valence as estimated in a small study (267) and for aversive (vs. neutral) pictures (978).

Further studies led to the assumption that OXT is particularly important for the recognition of social cues (e.g., faces) but not for non-social cues (colors, objects). In some studies, this difference was found to be independent of gender and emotional expression of the faces (459, 464, 872), whereas others showed a gender difference in the effects of OXT on social memory abilities (437) and on social cognition (276, 277, 671; for review, see Refs. 110, 405).

In addition to the gender studied, contrasting effects of OXT on learning, memory, and social recognition were generally found to be dependent on the timing of i.n. OXT application, i.e., whether treatment was performed during pre- or post-memory encoding, post-learning, or the retrieval phases. Moreover, OXT effects were found to be dependent on the dose and the treatment regime, i.e., whether single or repeated application of i.n. OXT was used (156, 1082; for review, see Ref. 110).

In summary, the reported findings in humans suggest that i.n. OXT selectively improves processes of attention, and recognition of and memory for socially relevant and emotional information, but may negatively affect non-emotional, non-social information processing. However, since the emerging picture is rather complex, thorough investigation of possible amnestic and promnestic effects of OXT, in a dose- and sex-dependent manner, are essential before repeated or intermittent application of OXT can be considered a safe treatment option for various psychiatric diseases accompanied by memory dysfunctions (195, 694, 753).

Overall, considering both animal and human studies, the emerging picture indicates that OXT is a substantial modulator of memory storage and recall, with the potential to improve processing of information with high biological relevance, i.e., in particular emotional and social information.

X. FOOD INTAKE AND SATIETY

A. OXT and Food Intake in Rodents

OXT has been considered to have potent anorectic properties and to play an important role in satiety and energy balance (for review, see Ref. 894). OXT neurons of the SON and PVN are regulated by appetite- and nutrition-related signals (362, 783, 859). For example, increased Fos protein expression—an indicator of elevated neuronal activity—has been found in OXT neurons of both the SON and PVN soon after the onset of food intake (495) by gastric distension and after administration of the satiety peptide CCK-8 (154, 859). Peripheral administration of CCK-8 was also reported to activate OXT secretion from the neurohypophysis into blood (574) and somato-dendritic release within the SON (742). In contrast, fasting resulted in reduced OXT expression in the PVN (569).

In this context, the PVN receives projections from various neuronal populations and brain regions, such as the primary leptin- and ghrelin-receptive neurons of the arcuate nucleus, orexigenic neurons co-expressing neuropeptide Y

(NPY) and agouti-related peptide, and pro-opiomelanocortin (POMC)-containing neurons in the arcuate nucleus, which also express the potent satiety peptide α-MSH (1041). In turn, the PVN regulates various aspects of the body's energy metabolism via *1*) thyreotropin releasing hormone-synthesizing neurons, regulating the thyroid gland and thyroxin release (14, 762), *2*) CRF neurons regulating pituitary ACTH and adrenal glucocorticoid secretion as major parts of the HPA axis (436), and *3*) the sympathetic nervous system (325). Specifically, parvocellular OXT neurons of the PVN project to the nucleus tractus solitarius (NTS) (873), where OXT was shown to modulate efferent vagal pathways that regulate gastric motility (675). Stimulation of PVN OXT neurons also inhibited gastric motility via the dorsal motor nucleus of the vagus, which also contains OXTR (292, 341, 881). Thus these OXT neurons seem to be a critical part of the gastrointestinal-vago-vagal reflex and of a circuitry that is triggered by food intake, gastric distension, and the secretion of CCK-8 from the duodenum (341, 894). In turn, CCK-8 is likely to activate afferent vagal neurons, leading to activation of brain stem structures, specifically within the NTS (940), which itself is densely innervated by OXT fibers originating from parvocellular OXT neurons of the PVN (88).

Regarding food intake, first studies from the 1980s demonstrated that lesion of hypothalamic nuclei containing OXT (but also other) neurons resulted in increased food intake and, consequently, elevated body weight gain (536, 605, 933, 941). In support, icv administration of synthetic OXT to rats at a relatively low dose was reported to inhibit food intake, and to delay the onset and reduce the duration of food intake independent of the satiety state of the animal (31, 783). Similarly, direct optogenetic activation of PVN OXT neurons resulted in suppressed food intake (42). Although chronic infusion of OXT into the brain reduced body weight gain in rats given a high-fat diet, it did not alter total food intake or the duration of food intake, which was in contrast to the reported acute effects of OXT. Instead, chronic OXT rather stimulated lipid metabolism in adipose tissue (249). OXT actions within the ventromedial nucleus of the hypothalamus are likely to underlie such effects and to contribute to the regulation of appetite, since the VMNH expresses OXTR at high density (1028). The ventromedial hypothalamus is particularly important for the regulation of energy balance, among others (see sect. VIII*A*).

Further support for OXT-induced suppression of food intake comes from OXTR- and OXT-deficient mice. Male (but not female) OXTR knockout mice developed an obese phenotype in later adulthood, despite food intake and motor activity being generally unchanged (990). Also, adult OXT knockout mice showed an elevation in body weight and fat stores without alterations in food intake or motor activity in both males and females (764).

In the context of its role in regulating general caloric metabolism, osmotic homeostasis, and sodium balance, it has to be mentioned that dehydration and systemic sodium loading are potent stimuli for the OXT (and AVP) system, resulting in elevated OXT secretion into blood and within the brain, while inhibiting appetite at the same time (340). Plasma OXT is likely to promote renal natriuresis (1061), whereas elevated OXT release in distinct brain regions as demonstrated in response to intraperitoneal hypertonic saline within the septum, dorsal hippocampus, and the SON (590, 743) may be part of a circuitry involved in the suppression of food intake and regulation of the body's osmotic homeostasis, at least in rodents.

As a final aspect of OXT regulating food intake and feeding behavior, its effects on the reward system have to be mentioned. Humans and other mammals alike are highly attracted by selected palatable foods, resulting in food intake just for pleasure, and not by metabolic demands. This is called hedonic feeding. As for any other hedonic behavior, hedonic feeding is thought to be associated with activation of the dopaminergic mesolimbic system originating from neurons in the ventral tegmental area and increased dopamine release within the nucleus accumbens, as discussed in detail below (see sect. XI). Briefly, OXT fibers from the PVN project to mesolimbic dopaminergic neurons (964, 979), and OXT was found to reduce drug-induced dopamine release within the nucleus accumbens (979). OXT-deficient mice have an enhanced preference selectively for, and consumption of, sweet solutions in the two-bottle choice test (21, 83), whereas no comparable effects on palatable high-fat liquid formulation was found (700). Several lines of evidence further suggest that regular sugar intake generally blunts the response of OXT neurons to food intake independent of the composition of the food. Well, in case you managed to read this extensive review until here, you deserve a large piece of German chocolate sent to you. However, OXT may also exert its satiating effect in dependence on specific components of diet rather than as a general effect (894).

In summary, the existing evidence supports the assumption that OXT plays an essential role in the inhibition of food intake via inhibition of food intake-induced activation of the reward system.

B. OXT and Food Intake in Humans

The role of OXT in food intake in humans has not been directly studied. Indirect evidence comes from studies describing an association of alterations in the gene coding for the transcription factor single-minded 1 (Sim1) and the development of obesity in humans (317, 450). A closer look at this gene in rodents indicates that Sim1 is expressed in the SON and PVN (699). Heterozygous Sim1 knockout mice (homozygous mice do not survive) were

reported to have low levels of OXT expression in the SON and PVN, are hyperphagic, and become obese (698), which can be reversed by icv OXT (569). In support of this, mice overexpressing Sim1 do not increase their food intake when they are given a high-fat diet; they are also resistant to diet-induced obesity (570).

More preliminary evidence for a role of OXT in food intake in humans comes from patients with Prader-Willi syndrome, who suffer from morbid obesity due to extreme hyperphagia. In postmortem tissue of a very small number of these patients, fewer OXT neurons were found within the hypothalamus (984), which supports the hypothesis of OXT being important to control and reduce food intake within physiological limits. This assumption is supported by findings in mice with knockout of genes associated with the Prader-Willi syndrome, which are characterized by hyperphagia and late-onset obesity, a deficient OXT synthesis in the hypothalamus (275), and reduced number of OXT neurons (730).

In contrast to the negative correlation between obesity and OXT in Prader-Willi patients, OXT levels in anorexia nervosa patients characterized by pathologically low amounts of food intake are lower compared with healthy controls (10). There are, however, contrasting reports regarding the correlation of symptoms of anorexia nervosa with anxiety and depression, with both negative (10) and positive (594) correlations being described. In a comprehensive meta-analysis, no correlation at all was found (891). In another eating disorder, bulimia nervosa, characterized by binge eating followed by purging, OXT plasma levels were not found to be correlated with the severity of the illness (712), indicating a specific role in the perception and regulation of pre- and post-meal-induced stress (594). In addition to plasma, urinary, and salivary OXT levels (448), OXTR polymorphisms (carrier of A allele in rs53576 and rs2254298) have also been linked with the severity of eating disorder symptoms (3).

XI. OXT AND ADDICTION

A. OXT and Addiction in Animal Studies

Substance-use disorders, or addictions, are severe, chronic brain disorders and major causes of global burden of disease (552). The use of tobacco, alcohol, and illicit substances was calculated to be responsible for a staggering 15% of all deaths worldwide each year (WHO 2012). However, treatment of these relapsing disorders is extremely limited. A growing body of evidence mainly from rodent studies suggests that the brain OXT system interacts with neuronal systems that underlie the development and maintenance of addiction, and that OXT may interfere with several stages of addiction, such as bingeing and intoxication, withdrawal and negative affect, and pre-occupation and anticipation that triggers relapse and further consumption (563).

Thus OXT was shown to reduce self-administration of alcohol or other drugs mostly shown after its peripheral administration in rodents. For example, heroin self-administration was inhibited by subcutaneous application of OXT or OXT fragments in heroin-tolerant male rats and mice (556, 557). Similarly, self-administration of stimulants, such as methamphetamine (160) and cocaine (75) was reduced by ip OXT in male Sprague-Dawley rats. OXT also inhibited self-administration of ethanol within 2–3 h, when applied ip to rats that had been chronically consuming ethanol in a continuous access paradigm (109).

We could recently also show that icv administration of OXT reduced alcohol consumption in male Wistar rats that had been consuming alcohol in a chronic intermittent consumption paradigm for 2 mo (816). This demonstrates that the described OXT effects on ethanol consumption are likely to be centrally mediated—at least in rats. In contrast, comparing ip vs. icv application of OXT in mice revealed that the inhibitory effect of OXT on ethanol consumption was only found after ip but not icv administration (814). Interestingly in this context, ip OXT reduced ethanol consumption only in non-stressed mice, but not in mice that were exposed to a chronic psychosocial stress paradigm for 3 wk (814, 816, 854). Although the underlying mechanisms of these contrasting effects are unknown, the discrepancy in the effectiveness of OXT in dependence of the mode of administration, i.e., central vs. peripheral, may be due to the different amounts of OXT applied ip vs. icv in that study.

Further evidence for an inhibitory effect of OXT on the rewarding effects of drugs has been revealed in the conditioned-place preference test. In this test, the preference of the experimental animal for an environment previously associated with the rewarding effects of a specific drug is assessed (563). OXT seems to be particular effective to attenuate the establishment of the place preference as well as to promote its extinction. Thus, applied either icv or ip, OXT inhibited the acquisition of methamphetamine-induced place preference and promoted the extinction of an established place preference, whereas it had no effect on the expression of an established methamphetamine-conditioned place preference (55, 848).

Interactions of OXT with the mesolimbic dopamine system, which is essential for the rewarding nature of drugs, and thus for addiction (552), are likely to underlie its effects on drug consumption and reward. OXT fibers terminate within the mesolimbic dopamine system, specifically in the nucleus accumbens (100, 161, 945), where it affects the drug-induced rise in dopamine signaling (563). For instance, OXT reduced the cocaine-induced increase in dopamine turnover in the nucleus accumbens and decreased

methamphetamine-induced activation of the nucleus accumbens (160, 847). Moreover, icv OXT completely blocked ethanol-induced dopamine release within the rat nucleus accumbens shell, after both acute and repeated ethanol administration (816). On a behavioral level, local infusion of OXT into the nucleus accumbens inhibited heroin self-administration in rats (559), attenuated the formation of a methamphetamine-conditioned place preference, and inhibited the reinstatement of methamphetamine-seeking (55, 56).

OXT was also found to attenuate the acute intoxicating effects of drugs, which include both hyper-locomotion and stereotyped behaviors (cocaine, ecstasy), as well as sedative and ataxic effects (alcohol, opioids). The sedative effects and the acute impairment of locomotor activity by ethanol are particularly dangerous and substantially contribute to alcohol-related injuries or even deaths. It has been shown that icv OXT reduced methamphetamine-induced hyper-locomotion and cocaine-induced stereotyped sniffing behavior in rats (160, 558, 847, 908). Moreover, an inhibition of the acute sedative, myorelaxant, and ataxic effects of ethanol by icv OXT has recently been reported in rats (109). The mechanism underlying this OXT effect on ethanol-induced locomotor impairment could be revealed to involve interactions with $GABA_A$ receptors (109). Activation of $GABA_A$ receptors with GABA generally underlies all ethanol effects, and OXT was found to completely block ethanol-$GABA_A$ receptor interactions and thus to prevent ethanol-induced locomotor dysfunctions. These effects were due to a direct, previously unknown, non-OXTR-mediated action at δ subunit-containing $GABA_A$ receptors (109).

Another important aspect of drug research in the context of OXT is its influence on the development of drug tolerance, whereas its effects on established tolerance seems minor (for review, see Refs. 161, 559). Thus OXT or its fragment administered sc or icv inhibited the development of tolerance to the hypothermic, ataxic, and myorelaxant effects of ethanol, the cocaine-induced stereotyped sniffing, and opioid-induced analgesia, in a dose-dependent manner. OXT also affects the opposite phenomenon, i.e., that drugs can induce behavioral sensitization, and OXT has been shown to rather facilitate the development of sensitization, as demonstrated in the context of hyper-locomotor effects of cocaine in mice (908).

OXT was further found to interfere with alcohol and drug withdrawal symptoms partly in a dose-dependent manner. For example, higher doses of sc OXT prolonged the onset of tonic seizures during ethanol withdrawal induced by picrotoxin in alcohol-dependent mice and reduced the withdrawal-induced mortality rate, with low doses showing the opposite effect (559). Also, ip OXT reduced nicotine withdrawal symptoms induced by an antagonist in nicotine-dependent rats (665). The withdrawal and negative affect stage of addiction is importantly characterized by severe alterations in emotionality, increased anxiety and stress responses, low mood, anhedonia, and loss of motivation for social interactions. As discussed above, OXT is considered an anxiolytic, anti-stress, and pro-social neuropeptide—in rodents and humans alike (see sect. VIII*F*); therefore, it has a great potential to interfere with long-lasting symptoms of drug withdrawal, particularly with emotional dysregulation, symptoms of stress, and social deficits. In support, ip injection of the OXT analog carbetocin reduced the level of withdrawal-induced anxiety and depression- and social anxiety-like behaviors in morphine-dependent mice. In the first human study on drug withdrawal, i.n. OXT applied to alcohol drinkers during ethanol withdrawal reduced anxiety and tension levels (810).

In this context, it is worth mentioning that morphine withdrawal induced by the opioid antagonist naloxone in morphine-dependent, anesthetized rats induced a supraphysiological activation of the endogenous OXT system, resulting in high levels of OXT release both from the neurohypophysis into blood and from soma and dendrites within the SON (890). However, whether morphine withdrawal also induces OXT release, for example, within the nucleus accumbens, or whether the profound OXT release described is a compensatory mechanism to cope with the withdrawal symptoms remains to be elucidated.

Considering the described effects of OXT in addiction, the question arises whether OXT also prevents relapse to drug consumption after periods of abstinence (563). Drug relapse in humans can be induced by stress or exposure to drug cues, and is a major clinical problem in the treatment of substance abuse. In preclinical models, OXT has also been shown to significantly interfere with drug relapse. For example, OXT at varying doses inhibited stress-induced reinstatement of methamphetamine-conditioned place preference in mice (848), the reinstatement of methamphetamine- and cocaine-seeking (55, 75, 160, 208, 721), and cocaine cue-induced anxiety (721) in rats. Whereas most of the studies on the effects of OXT on addiction were performed in male rodents, the effects of OXT on stress-, prime-, and cue-induced reinstatement of methamphetamine-seeking were found to be sex-dependent (208). Also, a long-lasting reduction in alcohol consumption and preference were described in male and female alcohol-preferring rats, further suggesting that OXT may support long-term abstinence (681).

Glutamatergic projections from the prefrontal cortex to the nucleus accumbens and ventral tegmental area are suggested to control neuronal activity in the nucleus accumbens and thus to control prime- and cue-induced reinstatement of drug seeking (370, 552). Indeed, OXT was reported to suppress glutamatergic transmission in the infralimbic prefrontal cortex (370), which may provide an underlying mechanism of the above-described effects of OXT on drug

reinstatement. In contrast, stress-induced reinstatement of drug seeking should rather be mediated by the activation of CRF and other stress-related systems in the amygdala. Therefore, OXT effects on stress-induced relapse are likely due to actions on the CRF system within the hypothalamus (221, 499) or the amygdala (544). Moreover, OXT may enforce the connectivity between the frontal cortex and amygdala (763), and the cortical control over stress-induced behavioral impulses (563).

According to another hypothesis, OXT may promote a switch from seeking out object-based rewards (such as drugs) to pursuing social reinforcement (681). In support, OXT infused into the prefrontal cortex reestablished normal social behavior in parallel to restoring normal baseline functioning of the nucleus accumbens dopamine system in prairie voles that had been chronically exposed to amphetamine (1118).

B. Clinical Studies on OXT and Drugs of Abuse, and Other Clinical Trials on OXT

To date, the number of clinical studies performed on patients with substance-abuse disorders is very limited. In a randomized double-blind placebo-controlled trial, i.n. OXT inhibited stress-induced craving in cannabis-dependent humans (684). Also, alcoholics undergoing medical detoxification required less lorazepam during treatment, had less severe withdrawal symptoms including reduced anxiety and tension levels, and had inhibited alcohol craving after i.n. OXT (810). OXT also specifically reduced alcohol cue-induced craving in alcohol users (without alcohol-use disorder) with an anxious attachment style, whereas the opposite was found in individuals with less anxious attachment (701). Rather complex results were found with i.n. OXT effects on cocaine-, heroin-, or opioid-induced craving (602).

Although there are currently 11 registered clinical trials, including exploratory and phase I, II, III, and IV clinical trials, which explore intranasal OXT as a treatment for substance-use disorders, specifically investigating the effects of i.n. OXT on nicotine, opioid, alcohol, amphetamine, cocaine, and marijuana dependence (108), more clinical studies are needed before i.n. OXT can be safely used in patients with drug-abuse disorders.

In this context, it should be noted that there are currently 564 registered clinical trials on OXT, with at least 171 examining the effects of i.n. OXT (www.clinicaltrials.gov/ct2/results?term=oxytocin&pg=1) on all different aspects of social and emotional behavior, genetics, intracerebral activity patterns (fMRI), and reproductive physiology, both under healthy and disease conditions. For example, trials are listed in the context of i.n. OXT as a treatment option for general anxiety disorder, major depressive disorder, Prader-Willi-syndrome, sexual dysfunction, trauma, or various substance-use disorders (see sect. XIII and Box 4).

XII. OXTR SNPs AND ASSOCIATED PSYCHOLOGICAL TRAITS

Single nucleotide polymorphisms (SNP) are variations of single nucleotides that occur at distinct positions in the genome with a frequency of occurrence larger than 1% of a certain population (https://ghr.nlm.nih.gov/primer/genomicresearch/snp). Each identified SNP is encoded with a unique reference number, for instance rs53576, and can be found in online databases (www.snpedia.com; www.ensembl.org). According to the "ensembl" database, the human *OXTR* gene contains 367 variations of different types (also see **FIGURE 13**). However, only a subset seems to affect the phenotype or behavior, and therefore we focused only on those in this review. The human haplotype map project (353) revealed several dozen SNPs in the *OXTR* that have been genotyped in association studies of various traits and behaviors in humans. Various *OXTR* SNPs have been, among others, associated with generous behavior (479), social behavior (547), empathy and social communication (1021), amygdala and hypothalamus functioning (1021), reduced physiological reactivity to stress (879), increased benefits from social support (175), and greater parenting sensitivity (46).

A. *OXTR* SNPs and Autism Spectrum Disorder

However, the most intensely studied and controversially discussed association is that of *OXTR* SNPs and autism spectrum disorder (ASD) (47, 802, 992). In this context, the question of particular importance is whether variations in the *OXTR* gene (intronic and exonic) are associated with various symptoms of ASD. Although researchers have estimated the heritability of ASD as being between 55 and 80% (633), there is a considerable heterogeneity among studies regarding the evidence peaking in favor of or against an association of *OXTR* SNPs and ASD. For instance, a significant correlation between *OXTR* rs237887 and face recognition was detected in ASD patients using the so-called Warrington Recognition Memory Test for faces (946); however, when other tests for face recognition were applied (Cambridge Face Memory, Mooney Face Test, Glasgow Face Matching Test, Composite Face Test), no correlation could be detected anymore (1063). Another recent study found that *OXTR* SNPs and plasma OXT level predict social impairments in children with or without ASD (802). These contradictory results implicate that the presence of a specific *OXTR* SNP identified in ASD patients does not necessarily contribute to the etiology of ASD.

Therefore, meta-analyses have been conducted to determine whether SNPs in the *OXTR* gene are indeed linked to symp-

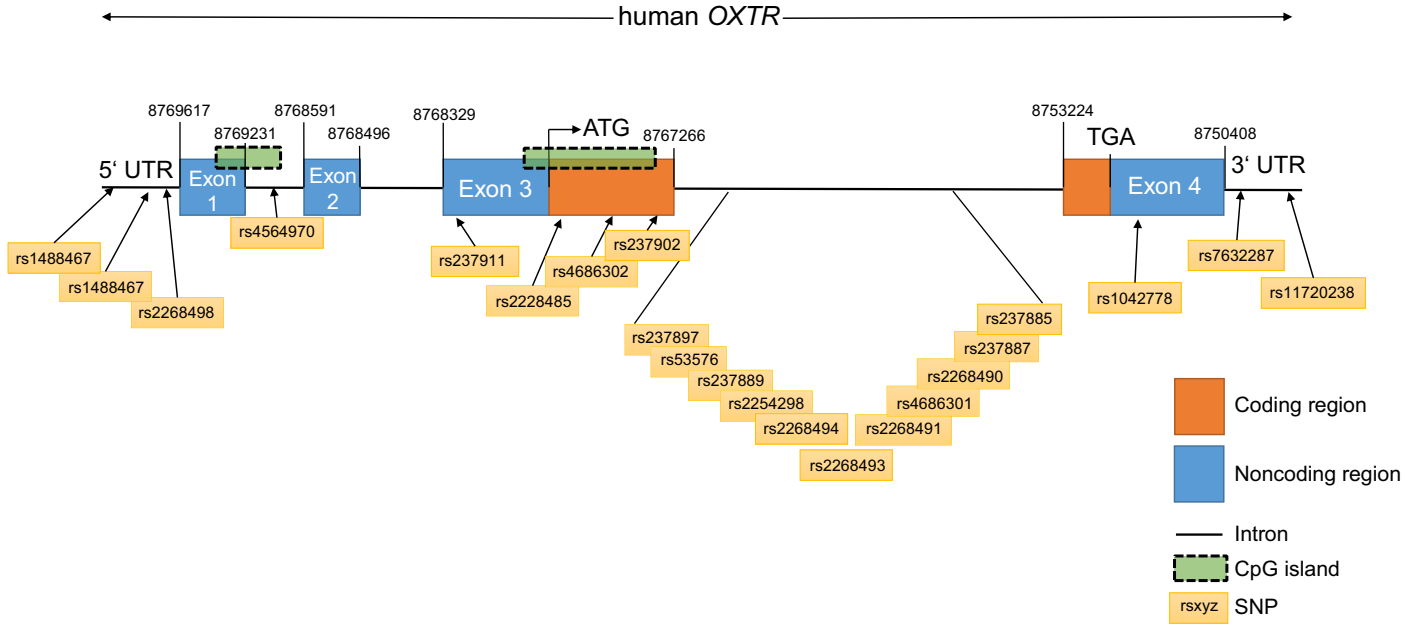


FIGURE 13. Structure of the human OXTR gene on *chromosome 3* with four exons (positions indicated above), three introns, position of SNPs, and CpG islands. Only SNPs that have been associated with psychological or psychiatric traits have been included. The total number of annotated variations within the OXTR gene is 367, including missense, synonymous, frameshift, and coding sequence variant, but also stop gain and inframe deletion. Data extracted from ensembl data base.

toms of ASD. One recent meta-analysis of 16 *OXTR* SNPs included 3,941 individuals with ASD. The authors found a significant association between ASD and the SNPs rs7632287A, rs237887A, rs2268491T, and rs2254298A (633). One SNP, rs7632287A, was located in the promoter region of the *OXTR*, where it may potentially alter transcription factor binding and therefore expression of the *OXTR*. However, experimental evidence regarding the functional significance of this SNP is still missing. In continuation of this study, a second meta-analysis corroborated the finding of LoParo and Waldman by adding data from five so far unpublished studies on ASD patients (562). Remarkably, the authors call for functional studies to "delineate the neurobiological implications of this and other association findings" (562).

B. *OXTR* SNPs and Other Psychological Traits

Although human research has mostly addressed the association between autism and two *OXTR* SNPs, i.e., rs53576A and rs2254298A, fewer studies focused on other *OXTR* (rs7632287A, rs1042778, rs2268494, rs2268490), *OXT* (rs2740210, rs4813627, rs4813625), and *CD38* (rs3796863, rs6449197) SNPs (322) in the context of other psychological traits such as trait empathy, depression, bulimia nervosa, or style of parenting (also see **TABLES 6**, **7**, and **8**). For instance, the rs53576 SNP is an intronic silent G to A change in the *OXTR* gene on *chromosome 3*. Although silent, a large number of studies has associated this SNP with mostly adverse psychological traits. Carriers of the A allele are associated with greater levels of loneliness (1048), symptoms of emotional withdrawal (418), impaired sociability (1021), seeking of social support at times of distress (527), decreased empathy (879), and decreased maternal sensitivity (46). In contrast to A allele carriers, two independent studies could demonstrate that SNP rs53576 GG predicts aggression or antisocial behavior under circumstances of high social stress in females (127, 952).

The variability in the *OXTR* gene (concerning following SNPs: rs75775, rs1488467, rs4564970, rs4686302, rs237897, rs53576, rs2254298, rs2268493, rs237887, rs1042778, rs7632287, rs11720238) has been found to strongly predict aggressive behavior in competitive computer games (632). However, the emerging picture on specific SNPs underlying aggression or antisocial behavior is rather complex; an association between SNP rs237885AA and high "callous and unemotional" traits was found within high-aggressive subjects (68), whereas a direct link between SNPs rs237898A and rs237902C and high aggression was found in boys (663). Furthermore, SNP rs1042778TT was found to be associated with high aggression in boys and girls with conduct problems (223) as well as with increased amygdala activation, when exposed to angry faces in men (1074). High amygdala activation is considered to be an established neuropsychological marker of antisocial behavior. SNP rs7632287AA was strongly associated with *Life History of Aggression* interview scores and *Self-Reported Delinquency* scores in two cohorts of

Table 6. *Publications on OXTR SNP rs53576 associations with psychological traits*

G Allele Carriers, Association With		A Allele Carriers, Association With	
Increased trusting (men, not women)	791	Higher scores on symptoms of emotional withdrawal	429
Higher susceptibility for bulimia nervosa in Korean women	547	Increased intergenerational transmission of depression	1036
Increased reward in social interactions (men)	327	Greater level of loneliness if social network is perceived negatively	1080
Increased susceptibility to social ostracism	705	Decrease in hypothalamic gray matter, increase in amygdala gray matter in males	1053
Impaired affect recognition	828	Higher social support seeking at times of distress	542
Maltreated children perceive lower social support in adolescence	466	ADHD children have better cognitive ability	827
Higher general psychopathology scores	737	Decreased empathy	907
Increased symptoms of depression in maltreated children	706	Decreased maternal sensitivity	44
Higher trust behavior than A allele carriers	581		
Emotional dysregulation in urban African American children	110		

children representing the normal Swedish population (455). SNPs rs4564790C and rs1488467C were predictive of higher levels of aggression, as measured in a competitive computer game and various questionnaires, but only in adult males who were under the influence of alcohol (491, 492).

These phenotypes were related to behavior by the Tridimensional Personality Questionnaire to quantify the effects of the SNP on self-reported prosocial temperament (1021). The association between the SNP and the self-reported social behavior was sex-specific, since it was absent in females (1021). There is some evidence for a mechanistic cause of the association between *OXTR* SNPS and these psychological traits. Tost and colleagues found, using the voxel based morphometry method, that male rs53576A allele carriers have an increased amygdala gray matter volume, whereas the gray matter volume in the hypothalamus is decreased, compared with G allele carriers (1021). Using correlative structural covariance methods to map the connectivity between brain areas, the authors also found a better coupling of the amygdala to the hypothalamus in male risk allele carriers.

These sex-dependent consequences of the presence of rs53576A allele were also found in 9/11 victims, where the association between genotype and posttraumatic stress symptoms were assessed in a negative environment (e.g., personal conflicts) or under economic stress. For female risk allele rs53576A carriers, a negative social environment increased posttraumatic stress symptoms, regardless of the economic situation, whereas in male risk allele rs53576A carriers the daily functioning was most affected by economic stress, i.e., times of financial restraint (638).

Another SNP, rs2254298A, has been associated with higher plasma levels of OXT compared with GG carriers (324); however, a functional explanation how this SNP alters the secretion of OXT into the plasma has not been provided.

In general, the literature provides some evidence for the involvement of *OXTR*, *OXT*, or *cd38* SNPs in social behavior but also suggests that other factors, such as sex, origin, and early life experiences often confound attempts to replicate initial findings. In summary, the initial results provide evidence for associations between the genetic variations in the *OXTR* or *OXT* and various aspects of human social and stress-related behavior. However, the neuronal mechanisms underlying the contribution of particular SNPs to a behavioral phenotype are still unclear. For instance, it remains to be explained mechanistically whether or how those mostly silent and intronic SNPs may alter processes of gene transcription or translation, may alter intracellular trafficking and neuronal release, or may affect receptor binding or OXTR downstream signaling, and how those effects culminate in a change of gray matter volume or size of (only) the amygdala (see also sect. XIII).

There is initial evidence that one SNP (rs2268498) in the promoter region of the *OXTR* nearby a p300-responsive element regulates the expression level of the *OXTR* gene in hippocampal samples from human patients (861). Despite some limitations of the study (unknown sex and age of the patient, unknown subregion of the hippocampus), this is a

Table 7. *OXTR SNP localization within the gene and associated psychological traits*

SNP ID	Locus on *Chromosome 3*	Localization	Comment/Association Context
rs11720238	8749653	3′ UTR	Autism
rs7632287	8749760	3′ UTR	Trait empathy, pair bonding, social behavior, autism
rs1042778	8752859	Exon 4	Prosociality, autism
rs237885	8753857	Intron 3/4	Prosociality, schizophrenia
rs237887	8755356	Intron 3/4	Trait empathy, social behavior, autism
rs2268490	8755399	Intron 3/4	Prosociality
rs4686301	8756900	Intron 3/4	Schizophrenia
rs2268491	8758712	Intron 3/4	Autism, trait empathy
rs2268493	8759154	Intron 3/4	Trait empathy, affiliative behavior
rs2268494	8760360	Intron 3/4	Autism, empathy
rs2254298	8760542	Intron 3/4	Anxiety, ASD, depression, amygdala volume
rs237889	8760797	Intron 3/4	Autism, prosociality
rs53576	8762685	Intron 3/4	Silent G to A change, affect loneliness, autism, parenting style
rs237897	8766599	Intron 3/4	Trait empathy, prosociality
rs237902	8767498	Exon 3, coding sequence	Preterm birth, aggression, drug addiction, stress response
rs4686302	8767536	Exon 3, coding sequence	Trait empathy, preterm birth
rs2228485	8768017	Exon 3, coding sequence	Affect, loneliness and intelligence
rs237911	8768322	Exon 3, non-coding sequence	Preterm birth
rs4564970	8768722	Intron 1/2	Aggression and alcohol intake
rs2268498	8770725	5′ UTR	Social perception
rs1488467	8771545	5′ UTR	Aggression and alcohol intake
rs1488467	8771545	5′ UTR	Aggression and alcohol intake

SNPs are listed from 3′ to 5′ end, including SNPs in the 3′ and 5′ untranslated regions of the OXTR gene. Data extracted from http://www.ensembl.org and http://www.SNPedia.com.

promising first step toward a functional understanding of the results of genome wide association studies.

XIII. CONCERNS AND UNSOLVED ISSUES IN HUMAN AND ANIMAL OXT RESEARCH

The remarkable and still growing number of reports about intriguing effects of synthetic OXT on a number of human and animal social and cognitive behaviors as well as stress-related neuronal and physiological parameters reviewed above have recently brought about severe concerns. Although the main concerns, i.e., invalid statistical means and biased publication, also exist in other fields of psychology (48, 937) or neuroscience in general (141), the increasing number of studies on the overwhelming effects of i.n. OXT on human behavior attract massive interest and raise particular hope to many patients suffering from autism spectrum disorder, schizophrenia, social and other anxiety disorders, or drug-use disorders. Therefore, we are convinced that the OXT scientific community has a particular responsibility to publish scientifically, statistically, and methodologically sound results.

Given the complexity of OXT effects on behavior and brain functions, the concerns and unsolved issues sum-

Table 8. *Publications on OXTR SNP rs2254298 associations with psychological traits*

Allele Carrier, rs2254298	Association With	Reference
G allele	No effect on emotional withdrawal	429
A allele	Global social impairments	827
G allele	Smaller volume of amygdala, posterior brain stem, and dorsomedial anterior cingulate cortex	368
A allele	Increased attachment security in non-caucasian children	176
AA, AG	No effect on bulimia nervosa	547
CC, CT, TT	No effect on Alexithymia	565

marized below seem to be important and need to be resolved for the translational success of the OXT field.

A. Concerns Regarding Statistical Analyses

In the context of statistical analyses, Walum and colleagues carefully evaluated published results on i.n. OXT effects (1075). Their overall conclusion was that *1*) human i.n. studies are in most cases underpowered, *2*) the statistical means to present a selected data set are often invalid, and *3*) methodological approaches are often not validated. Although human studies are costly, even in studies with small sample sizes and low statistical power the scientific community expects a more critical and careful interpretation of the mostly positive results. Therefore, a healthy skepticism toward i.n. OXT studies is advisable, since Walum states a high probability that most of the published i.n. OXT findings do not represent true effects. In addition, failure to replicate a properly performed original study can be caused by an underpowered replication study. Recently, various suggestions were published to increase the trustworthiness and reliability of OXT-related research in humans (141, 607, 1075). These include the performance of a priori power calculations and, consequently, the performance of sufficiently powered original and replication studies by increasing the sample size. This could be achieved, for example, by collaboration of several research teams and statistical combination of their volunteer or patient cohorts, provided identical experimental protocols have been employed.

B. Concerns Regarding Biased Results

The necessity for healthy skepticism is highlighted by the overwhelming and almost exclusive pro-social and other positive effects of i.n. OXT reported in highly ranked journals: from increasing social trust, improving romantic relationships, and maternal and paternal interactions with the child, to promoting empathy and altruism. In addition, it attenuates withdrawal-induced symptoms in alcoholics, often with one behavioral parameter only slightly changed, and only under very specific experimental conditions. It seems that i.n. OXT is capable of doing it all. In other words, as Walum and colleagues wrote, "If all of the conclusions from human OXT research were true, one might characterize OXT as the elixir of the social brain" (1075). Publications that fail to report an OXT effect or report on negative effects are largely missing. Therefore, the publication of positive, negative, and null results should strongly be encouraged to correct the emerging picture of OXT, also in the popular press.

C. Concerns Regarding the Amount of OXT Applied Intranasally

The value and interpretation of human or animal studies using supraphysiological amounts of OXT applied i.n. have been identified as another major concern (607). The authors argued that the human pituitary contains ~14 IU of OXT, as estimated by a bioassay; thus, given the biological activity of synthetic OXT in the range of 500 IU/mg, and the molecular weight of the OXT molecule of 1,007 g/mol, the human pituitary content is ~28 μg OXT. In most human studies, OXT is applied i.n. in amounts of 24 IU (i.e., 48 μg), which exceeds the entire pituitary content and results in supraphysiological amounts of the nonapeptide in the body. Despite this, only a very small percentage of synthetic OXT (0.002%) can be found in the brain cerebrospinal fluid (693). Here, the question arises about the fate of these large amounts of OXT applied. *1*) Most of the i.n. applied OXT will be swallowed, thus, reaching the mouth cavity (and can be found in massive amounts in the saliva), will enter the intestinal tract, where it will be digested, fragmented, and excreted. *2*) Another large portion enters the blood stream via nasal or mouth endothelial capillaries and thus will target all peripheral OXTR, which are abundantly expressed in various peripheral organs, such as heart, skin, intestinal tract, or autonomic nervous system (see sect IV*F*). To which extent peripheral OXTR-mediated mechanisms contribute to the observed central effects of OXT is still a matter of debate (see below). *3*) Most importantly, only a minor part of the applied OXT will indeed enter the brain compartment, although the routes of transport are still a matter of debate (see sect. XIII*F*). Since the blood-brain-barrier efficiently protects against the uptake of peripherally circulating peptides, at least at physiological concentrations (315) it has been estimated that only a very limited amount of i.n. OXT [estimated to be 0.002–0.005% at best (226, 607, 693, 754] has access to the brain compartment. Therefore, it seems likely that the high doses of OXT applied i.n. are in fact needed for the many observed central and behavioral effects. To provide evidence for this hypothesis, proper dose-response studies are essentially needed, especially those using significantly lower doses of i.n. OXT, i.e., one to two orders of magnitude lower than the dose of 24 IU most frequently used.

D. Concerns Regarding OXT Assays

Another major concern of human and animal OXT research alike is the quantification of endogenous OXT in various body fluids (saliva, plasma, urine, CSF). Originally, OXT has been assessed by a bioassay in mammary or myometrial tissue, but soon a sensitive radioimmunoassay (RIA) was established in the 1970s and 1980s (173, 181, 230, 583). Later, competitive enzyme-linked immunosorbent assays (ELISA), immunosensing with microdialysis probes containing antibody-based electrodes, and capillary

liquid chromatography combined with electrospray ionization-mass spectrometry (202, 585) were developed, suitable for quantifying plasma OXT (839). Sandwich ELISAs are increasingly commercially available; however, the quality of these assays depends on the affinity and specificity of the antibody used. In recent studies, a tandem liquid chromatography and mass spectrometry (LC/MS) has also been successfully used to assess OXT quantities (1134).

There is a general agreement that physiological OXT concentrations in the plasma are in the range of 0.1–10 pg/ml, which has repeatedly been validated by bioassays, RIA, and LC/MS by means of physiological stimuli known to trigger OXT secretion into blood. However, to yield reliable and physiological concentrations of OXT in blood, e.g., from humans, monkeys, rats, or mice, plasma samples need to be essentially extracted to eliminate potentially interfering plasma proteins, which is also highly recommended by the respective suppliers (see, for example, http://www.enzolifesciences.com/fileadmin/redacteur/pdf/adi/ADI-900-153.pdf). Thus, in unextracted plasma samples, OXT concentrations were found to be 100–1,000-fold higher than measurements in extracted samples (607, 680, 878), and such supraphysiological high levels are clearly due to substances other than OXT. As a consequence, parallel analysis of plasma samples by ELISA with and without prior extraction procedure did not reveal any correlations (878, 982, 987).

Although the high concentrations of OXT in unextracted plasma samples may reflect both free, i.e., biologically active, as well as binding protein-bound OXT, as revealed by the use of a nano LC/MS platform (112), the origin and biological relevance of bound OXT is questionable.

Importantly, OXT in saliva can be assayed without prior extraction procedure (237). This fact, in combination with the convenient sampling procedure, especially for patients or young volunteers, makes saliva OXT an interesting alternative to assess the dynamics of peripheral OXT levels (237).

In summary, the use of inappropriate and questionable detection assays strongly contributes to uncertainties among OXT researchers. Thus the extension of existing and further development of highly sensitive, specific, accessible, and affordable OXT assays for the reliable and standardized quantification of OXT represents one central objective for OXT research.

E. Concerns Regarding the Interpretation of Peripheral OXT Levels

In this context, another concern of human and animal OXT research needs to be mentioned. Due to limited access to CSF or brain extracellular fluid, which can be collected more easily in animals, most human (but also many animal) studies rely exclusively on peripheral OXT analyses, i.e., blood and saliva. However, caution is warranted when it comes to the interpretation of OXT levels in peripheral fluids. As discussed above, OXT secretion into blood from neurohypophysial terminals was found to occur simultaneously to, but also independently of, intracerebral release. Although a stimulated increase in plasma OXT has been shown to be accompanied by an increase in OXT release within distinct brain regions (e.g., during suckling, birth, stress, exercise) (591, 753), some stimuli also trigger central, but not peripheral, OXT release. In addition, release within the brain and into the blood occurs in differential temporal patterns (see above). Moreover, OXT release into blood and brain has never been consistently monitored and compared under basal conditions. Consequently, information is lacking, whether basal plasma or saliva OXT reflects the fine-tuned basal OXT release within distinct brain regions. Thus elevated levels of OXT in blood sampled under resting conditions, for example in patients suffering from anxiety disorders, would be an unreliable predictor for elevated brain OXT activity. Moreover, basal plasma or brain OXT levels might strongly depend on individual events occurring within the last hour(s) before sampling (e.g., fear of hospital or laboratory, prior eating, rushing to the laboratory, or sex) or on the time of the day. One possibility to circumvent this concern is, in addition to baseline, to stimulate the OXT system under defined experimental conditions, thus revealing the true responsiveness of the OXT system, as reflected by increased OXT concentrations in plasma or saliva in distinct patient cohorts and healthy controls. Recently, the Regensburg Oxytocin Challenge (ROC) test was established, demonstrating reliable increases in OXT saliva levels sampled from healthy volunteers in response to physical exercise (10 min of running), sexual stimulation, and the TSST. Whether the ROC test or another adapted OXT challenge test is suitable as routine test for the assessment of the OXT system responsiveness needs to be shown. In this context, it is interesting to note that, so far, no diurnal rhythm of OXT release within the PVN or SON has been detected, and OXT release from the suprachiasmatic nucleus, as the pacemaker of diurnal rhythms, was below the detection limit (504, but also see Refs. 655, 1133).

An alternative approach to the above-discussed scenario is to measure OXT in CSF, which might better reflect its availability in the brain (502). However, regional fluctuations in OXT levels will essentially be ignored. Furthermore, this invasive method is not feasible for routine use in humans.

Generally, engaging the endogenous OXT system in human studies on OXT, for example by assessing OXT

concentrations in body fluids or genetic variations in the *OXTR*, would be a step forward for the field. In this way, we may be able to distinguish between individuals who respond to i.n. OXT treatment (OXT responders) and those who do not (OXT non-responders), possibly based on differences in the endogenous OXT activity.

F. Unknown Routes of Uptake or Information Transfer of i.n. OXT to the Brain

The routes of uptake of OXT into the brain are completely speculative and, therefore, still a matter of concern. Thus several possible transport routes of synthetic i.n.-applied OXT (and other peptides) from the nasal mucosa to the brain have been critically discussed (263, 607, 753, 754). They include *1*) uptake into the olfactory and trigeminal nerves connecting the nasal passage to the olfactory bulb and other central targets, *2*) uptake via vascular connections from the nasal mucosa with high density of capillaries, and *3*) limited OXT transport across the blood-brain barrier after uptake of i.n.-applied OXT into peripheral blood circulation with the limitations discussed above. Moreover, the role of circumventricular organs lacking the blood-brain barrier (including choroid plexus, pituitary and pituitary stalk, organum vasculosum of the lamina terminalis, subfornical organ, area postrema, and subcommisural organ) (9, 954, 1116), where OXTR are also expressed, and their neuronal connections to various hypothalamic and other brain regions need to be seriously considered.

In an attempt to monitor the uptake of OXT after i.n. application of supraphysiological amounts, OXT has been analyzed in CSF and brain extracellular fluid [as measured by microdialysis (754)] in both animal (rats, mice, macaques) and human studies. However, rather inconsistent results were reported (96, 226, 704, 754), which were only consistent in the demonstration that a maximal central uptake of 0.005% of applied OXT can be achieved.

In contrast, i.n. OXT has consistently been shown to result in elevated plasma OXT concentrations. Therefore, OXT interactions with OXTR in the periphery, for example at gastric vagal nerve endings (482) or in the heart (515), need to be seriously considered as a plausible mechanism of action of i.n. OXT transferring the peripheral OXT signal to the brain. As reviewed above (see sect. X), peripheral OXT was described to regulate metabolic processes including the secretion of insulin and glucagon (18), gastric motility (1085), activation of vagal afferent neurons (482), and increasing heart rate variability after i.n. application in humans (515).

G. Unknown Mechanisms of Association Between OXTR SNPs and Psychological Traits

A high level of uncertainty also exists regarding the functional impact of associations between SNPs described in the *OXTR* gene and various behavioral traits (see above), including the degree of loneliness (1048), symptoms of emotional withdrawal (418), sociability (1021), empathy (879), maternal sensitivity (46), aggression and antisocial behavior (127, 952), or plasma levels of OXT (324). Although some data on the functional relevance of a SNP residing in the promoter region has been published (888), it is completely unknown how the mostly silent and intronic SNPs that are mainly associated with psychological traits (e.g., rs53576, rs2254298) affect OXTR physiology and functioning, for example OXTR expression, ligand affinity and binding capacity, or OXTR-coupled intraneuronal signaling cascades.

ACKNOWLEDGMENTS

We apologize to all of our wonderful colleagues in the field who we were not able to mention or whose important results could not be adequately cited mainly due to space restrictions and keeping the review in a readable format. We specifically thank Rainer Landgraf for critically reading the entire text, and many of our dear colleagues of the Department of Behavioral and Molecular Neurobiology, who critically read specific paragraphs or provided valuable comments.

GRANTS

This review was supported by DFG (B.J., I.D.N), BMBF (OptiMD; I.D.N.), and EU (FemNat-CD; I.D.N.).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES

1. Acevedo-Rodriguez A, Mani SK, Handa RJ. Oxytocin and estrogen receptor β in the brain: an overview. *Front Endocrinol (Lausanne)* 6: 160, 2015. doi:10.3389/fendo.2015.00160.

2. Acevedo BP, Aron A, Fisher HE, Brown LL. Neural correlates of long-term intense romantic love. *Soc Cogn Affect Neurosci* 7: 145–159, 2012. doi:10.1093/scan/nsq092.

3. Acevedo SF, Valencia C, Lutter M, McAdams CJ. Severity of eating disorder symptoms related to oxytocin receptor polymorphisms in anorexia nervosa. *Psychiatry Res* 228: 641–648, 2015. doi:10.1016/j.psychres.2015.05.040.

4. Acher R, Chauvet J, Chauvet MT. Man and the chimaera. Selective versus neutral oxytocin evolution. *Adv Exp Med Biol* 395: 615–627, 1995.

5. Acher R, Chauvet J, Chauvet MT. Phylogeny of the neurohypophysial hormones. *Nature* 216: 1037–1038, 1967. doi:10.1038/2161037a0.

6. Acheson D, Feifel D, de Wilde S, McKinney R, Lohr J, Risbrough V. The effect of intranasal oxytocin treatment on conditioned fear extinction and recall in a healthy human sample. *Psychopharmacology (Berl)* 229: 199–208, 2013. doi:10.1007/s00213-013-3099-4.

7. Ackerman AE, Lange GM, Clemens LG. Effects of paraventricular lesions on sex behavior and seminal emission in male rats. *Physiol Behav* 63: 49–53, 1997. doi:10.1016/S0031-9384(97)00386-7.

8. Adan RA, Cox JJ, Beischlag TV, Burbach JP. A composite hormone response element mediates the transactivation of the rat oxytocin gene by different classes of nuclear hormone receptors. *Mol Endocrinol* 7: 47–57, 1993.

9. Adan RA, Van Leeuwen FW, Sonnemans MA, Brouns M, Hoffman G, Verbalis JG, Burbach JP. Rat oxytocin receptor in brain, pituitary, mammary gland, and uterus: partial sequence and immunocytochemical localization. *Endocrinology* 136: 4022–4028, 1995. doi:10.1210/endo.136.9.7649111.

10. Afinogenova Y, Schmelkin C, Plessow F, Thomas JJ, Pulumo R, Micali N, Miller KK, Eddy KT, Lawson EA. Low fasting oxytocin levels are associated with psychopathology in anorexia nervosa in partial recovery. *J Clin Psychiatry* 77: e1483–e1490, 2016. doi:10.4088/JCP.15m10217.

11. Akerlund M, Bossmar T, Brouard R, Kostrzewska A, Laudanski T, Lemancewicz A, Serradeil-Le Gal C, Steinwall M. Receptor binding of oxytocin and vasopressin antagonists and inhibitory effects on isolated myometrium from preterm and term pregnant women. *Br J Obstet Gynaecol* 106: 1047–1053, 1999. doi:10.1111/j.1471-0528.1999.tb08112.x.

12. Alcorn JL III, Green CE, Schmitz J, Lane SD. Effects of oxytocin on aggressive responding in healthy adult men. *Behav Pharmacol* 26: 798–804, 2015. doi:10.1097/FBP.0000000000000173.

13. Alcorn JL III, Rathnayaka N, Swann AC, Moeller FG, Lane SD. Effects of intranasal oxytocin on aggressive responding in antisocial personality disorder. *Psychol Rec* 65: 691–703, 2015. doi:10.1007/s40732-015-0139-y.

14. Alkemade A. Central and peripheral effects of thyroid hormone signalling in the control of energy metabolism. *J Neuroendocrinol* 22: 56–63, 2010. doi:10.1111/j.1365-2826.2009.01932.x.

15. Altemus M, Deuster PA, Galliven E, Carter CS, Gold PW. Suppression of hypothalmic-pituitary-adrenal axis responses to stress in lactating women. *J Clin Endocrinol Metab* 80: 2954–2959, 1995.

16. Altirriba J, Poher AL, Caillon A, Arsenijevic D, Veyrat-Durebex C, Lyautey J, Dulloo A, Rohner-Jeanrenaud F. Divergent effects of oxytocin treatment of obese diabetic mice on adiposity and diabetes. *Endocrinology* 155: 4189–4201, 2014. doi:10.1210/en.2014-1466.

17. Altstein M, Gainer H. Differential biosynthesis and posttranslational processing of vasopressin and oxytocin in rat brain during embryonic and postnatal development. *J Neurosci* 8: 3967–3977, 1988.

18. Altszuler N, Hampshire J. Intranasal instillation of oxytocin increases insulin and glucagon secretion. *Proc Soc Exp Biol Med* 168: 123–124, 1981. doi:10.3181/00379727-168-41245.

19. Alvares GA, Chen NT, Balleine BW, Hickie IB, Guastella AJ. Oxytocin selectively moderates negative cognitive appraisals in high trait anxious males. *Psychoneuroendocrinology* 37: 2022–2031, 2012. doi:10.1016/j.psyneuen.2012.04.018.

20. Amico JA, Mantella RC, Vollmer RR, Li X. Anxiety and stress responses in female oxytocin deficient mice. *J Neuroendocrinol* 16: 319–324, 2004. doi:10.1111/j.0953-8194.2004.01161.x.

21. Amico JA, Vollmer RR, Cai HM, Miedlar JA, Rinaman L. Enhanced initial and sustained intake of sucrose solution in mice with an oxytocin gene deletion. *Am J Physiol Regul Integr Comp Physiol* 289: R1798–R1806, 2005. doi:10.1152/ajpregu.00558.2005.

22. Amsalem H, Aldrich CJ, Oskamp M, Windrim R, Farine D. Postpartum uterine response to oxytocin and carbetocin. *J Reprod Med* 59: 167–173, 2014.

23. Aragona BJ, Liu Y, Curtis JT, Stephan FK, Wang Z. A critical role for nucleus accumbens dopamine in partner-preference formation in male prairie voles. *J Neurosci* 23: 3483–3490, 2003.

24. Arakawa H, Blanchard DC, Blanchard RJ. Central oxytocin regulates social familiarity and scent marking behavior that involves amicable odor signals between male mice. *Physiol Behav* 146: 36–46, 2015. doi:10.1016/j.physbeh.2015.04.016.

25. Argiolas A, Collu M, Gessa GL, Melis MR, Serra G. The oxytocin antagonist d(CH2)5Tyr(Me)-Orn8-vasotocin inhibits male copulatory behaviour in rats. *Eur J Pharmacol* 149: 389–392, 1988. doi:10.1016/0014-2999(88)90675-9.

26. Argiolas A, Melis MR. Neuropeptides and central control of sexual behaviour from the past to the present: a review. *Prog Neurobiol* 108: 80–107, 2013. doi:10.1016/j.pneurobio.2013.06.006.

27. Argiolas A, Melis MR, Gessa GL. Intraventricular oxytocin induces yawning and penile erection in rats. *Eur J Pharmacol* 117: 395–396, 1985. doi:10.1016/0014-2999(85)90018-4.

28. Argiolas A, Melis MR, Stancampiano R, Gessa GL. Penile erection and yawning induced by oxytocin and related peptides: structure-activity relationship. *Peptides* 10: 559–563, 1989. doi:10.1016/0196-9781(89)90142-3.

29. Arima H, Aguilera G. Vasopressin and oxytocin neurones of hypothalamic supraoptic and paraventricular nuclei co-express mRNA for Type-1 and Type-2 corticotropin-releasing hormone receptors. *J Neuroendocrinol* 12: 833–842, 2000. doi:10.1046/j.1365-2826.2000.00528.x.

30. Arletti R, Bazzani C, Castelli M, Bertolini A. Oxytocin improves male copulatory performance in rats. *Horm Behav* 19: 14–20, 1985. doi:10.1016/0018-506X(85)90002-9.

31. Arletti R, Benelli A, Bertolini A. Oxytocin inhibits food and fluid intake in rats. *Physiol Behav* 48: 825–830, 1990. doi:10.1016/0031-9384(90)90234-U.

32. Arletti R, Benelli A, Bertolini A. Oxytocin involvement in male and female sexual behavior. *Ann N Y Acad Sci* 652: 180–193, 1992. doi:10.1111/j.1749-6632.1992.tb34354.x.

33. Arletti R, Benelli A, Bertolini A. Sexual behavior of aging male rats is stimulated by oxytocin. *Eur J Pharmacol* 179: 377–381, 1990. doi:10.1016/0014-2999(90)90178-9.

34. Arletti R, Benelli A, Poggioli R, Luppi P, Menozzi B, Bertolini A. Aged rats are still responsive to the antidepressant and memory-improving effects of oxytocin. *Neuropeptides* 29: 177–182, 1995. doi:10.1016/0143-4179(95)90021-7.

35. Arletti R, Bertolini A. Oxytocin acts as an antidepressant in two animal models of depression. *Life Sci* 41: 1725–1730, 1987. doi:10.1016/0024-3205(87)90600-X.

36. Armbruster BN, Li X, Pausch MH, Herlitze S, Roth BL. Evolving the lock to fit the key to create a family of G protein-coupled receptors potently activated by an inert ligand. *Proc Natl Acad Sci USA* 104: 5163–5168, 2007. doi:10.1073/pnas.0700293104.

37. Arosio A, Sala G, Rodriguez-Menendez V, Grana D, Gerardi F, Lunetta C, Ferrarese C, Tremolizzo L. MEF2D and MEF2C pathways disruption in sporadic and familial ALS patients. *Mol Cell Neurosci* 74: 10–17, 2016. doi:10.1016/j.mcn.2016.02.002.

38. Arsenijevic Y, Dreifuss JJ, Vallet P, Marguerat A, Tribollet E. Reduced binding of oxytocin in the rat brain during aging. *Brain Res* 698: 275–279, 1995. doi:10.1016/0006-8993(95)01020-V.

39. Arsenijevic Y, Tribollet E. Region-specific effect of testosterone on oxytocin receptor binding in the brain of the aged rat. *Brain Res* 785: 167–170, 1998. doi:10.1016/S0006-8993(97)01429-7.

40. Arvan P, Castle D. Sorting and storage during secretory granule biogenesis: looking backward and looking forward. *Biochem J* 332: 593–610, 1998. doi:10.1042/bj3320593.

41. Ashwin C, Baron-Cohen S, Wheelwright S, O'Riordan M, Bullmore ET. Differential activation of the amygdala and the 'social brain' during fearful face-processing in Asperger Syndrome. *Neuropsychologia* 45: 2–14, 2007. doi:10.1016/j.neuropsychologia.2006.04.014.

42. Atasoy D, Betley JN, Su HH, Sternson SM. Deconstruction of a neural circuit for hunger. *Nature* 488: 172–177, 2012. doi:10.1038/nature11270.

43. Augustine RA, Ladyman SR, Bouwer GT, Alyousif Y, Sapsford TJ, Scott V, Kokay IC, Grattan DR, Brown CH. Prolactin regulation of oxytocin neurone activity in pregnancy and lactation. *J Physiol* 595: 3591–3605, 2017. doi:10.1113/JP273712.

44. Ayar A, Ozcan M, Alcin E, Serhatlioglu I, Ozcan S, Kutlu S, Kelestimur H. Oxytocin activates calcium signaling in rat sensory neurons through a protein kinase C-depen-

dent mechanism. *J Physiol Biochem* 70: 43–48, 2014. doi:10.1007/s13105-013-0278-z.

45. Bai HY, Cao J, Liu N, Xu L, Luo JH. Sexual behavior modulates contextual fear memory through dopamine D1/D5 receptors. *Hippocampus* 19: 289–298, 2009. doi:10.1002/hipo.20505.

46. Bakermans-Kranenburg MJ, van Ijzendoorn MH. Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. *Soc Cogn Affect Neurosci* 3: 128–134, 2008. doi:10.1093/scan/nsn004.

47. Bakermans-Kranenburg MJ, van Ijzendoorn MH. A sociability gene? Meta-analysis of oxytocin receptor genotype effects in humans. *Psychiatr Genet* 24: 45–51, 2014. doi:10.1097/YPG.0b013e3283643684.

48. Bakker M, van Dijk A, Wicherts JM. The rules of the game called psychological science. *Perspect Psychol Sci* 7: 543–554, 2012. doi:10.1177/1745691612459060.

49. Bakos J, Lestanova Z, Strbak V, Havranek T, Bacova Z. Neonatal manipulation of oxytocin prevents lipopolysaccharide-induced decrease in gene expression of growth factors in two developmental stages of the female rat. *Neuropeptides* 48: 281–286, 2014. doi:10.1016/j.npep.2014.06.004.

50. Bakos J, Strbak V, Ratulovska N, Bacova Z. Effect of oxytocin on neuroblastoma cell viability and growth. *Cell Mol Neurobiol* 32: 891–896, 2012. doi:10.1007/s10571-012-9799-1.

51. Bale TL, Davis AM, Auger AP, Dorsa DM, McCarthy MM. CNS region-specific oxytocin receptor expression: importance in regulation of anxiety and sex behavior. *J Neurosci* 21: 2546–2552, 2001.

52. Bale TL, Dorsa DM. Regulation of oxytocin receptor messenger ribonucleic acid in the ventromedial hypothalamus by testosterone and its metabolites. *Endocrinology* 136: 5135–5138, 1995. doi:10.1210/endo.136.11.7588251.

53. Bale TL, Dorsa DM. Sex differences in and effects of estrogen on oxytocin receptor messenger ribonucleic acid expression in the ventromedial hypothalamus. *Endocrinology* 136: 27–32, 1995. doi:10.1210/endo.136.1.7828541.

54. Bales KL, Perkeybile AM, Conley OG, Lee MH, Guoynes CD, Downing GM, Yun CR, Solomon M, Jacob S, Mendoza SP. Chronic intranasal oxytocin causes long-term impairments in partner preference formation in male prairie voles. *Biol Psychiatry* 74: 180–188, 2013. doi:10.1016/j.biopsych.2012.08.025.

55. Baracz SJ, Everett NA, McGregor IS, Cornish JL. Oxytocin in the nucleus accumbens core reduces reinstatement of methamphetamine-seeking behaviour in rats. *Addict Biol* 21: 316–325, 2016. doi:10.1111/adb.12198.

56. Baracz SJ, Rourke PI, Pardey MC, Hunt GE, McGregor IS, Cornish JL. Oxytocin directly administered into the nucleus accumbens core or subthalamic nucleus attenuates methamphetamine-induced conditioned place preference. *Behav Brain Res* 228: 185–193, 2012. doi:10.1016/j.bbr.2011.11.038.

57. Barrett CE, Modi ME, Zhang BC, Walum H, Inoue K, Young LJ. Neonatal melanocortin receptor agonist treatment reduces play fighting and promotes adult attachment in prairie voles in a sex-dependent manner. *Neuropharmacology* 85: 357–366, 2014. doi:10.1016/j.neuropharm.2014.05.041.

58. Bartels A, Zeki S. The neural correlates of maternal and romantic love. *Neuroimage* 21: 1155–1166, 2004. doi:10.1016/j.neuroimage.2003.11.003.

59. Barth T, Krejcí I, Vaněcková J, Jost K, Rychlík I. Prolonged action of deamino-carba analogues of oxytocin on the rat uterus in vivo. *Eur J Pharmacol* 25: 67–70, 1974. doi:10.1016/0014-2999(74)90095-8.

60. Bartlett PJ, Metzger W, Gaspers LD, Thomas AP. Differential regulation of multiple steps in inositol 1,4,5-trisphosphate signaling by protein kinase C shapes hormone-stimulated Ca2+ oscillations. *J Biol Chem* 290: 18519–18533, 2015. doi:10.1074/jbc.M115.657767.

61. Baskerville TA, Allard J, Wayman C, Douglas AJ. Dopamine-oxytocin interactions in penile erection. *Eur J Neurosci* 30: 2151–2164, 2009. doi:10.1111/j.1460-9568.2009.06999.x.

62. Baskerville TA, Douglas AJ. Dopamine and oxytocin interactions underlying behaviors: potential contributions to behavioral disorders. *CNS Neurosci Ther* 16: e92–e123, 2010. doi:10.1111/j.1755-5949.2010.00154.x.

63. Bathgate R, Rust W, Balvers M, Hartung S, Morley S, Ivell R. Structure and expression of the bovine oxytocin receptor gene. *DNA Cell Biol* 14: 1037–1048, 1995. doi:10.1089/dna.1995.14.1037.

64. Baumgärtel K, Genoux D, Welzl H, Tweedie-Cullen RY, Koshibu K, Livingstone-Zatchej M, Mamie C, Mansuy IM. Control of the establishment of aversive memory by calcineurin and Zif268. *Nat Neurosci* 11: 572–578, 2008. doi:10.1038/nn.2113.

65. Bealer SL, Lipschitz DL, Ramoz G, Crowley WR. Oxytocin receptor binding in the hypothalamus during gestation in rats. *Am J Physiol Regul Integr Comp Physiol* 291: R53–R58, 2006. doi:10.1152/ajpregu.00766.2005.

66. Beery AK, McEwen LM, MacIsaac JL, Francis DD, Kobor MS. Natural variation in maternal care and cross-tissue patterns of oxytocin receptor gene methylation in rats. *Horm Behav* 77: 42–52, 2016. doi:10.1016/j.yhbeh.2015.05.022.

67. Behnia B, Heinrichs M, Bergmann W, Jung S, Germann J, Schedlowski M, Hartmann U, Kruger TH. Differential effects of intranasal oxytocin on sexual experiences and partner interactions in couples. *Horm Behav* 65: 308–318, 2014. doi:10.1016/j.yhbeh.2014.01.009.

68. Beitchman JH, Zai CC, Muir K, Berall L, Nowrouzi B, Choi E, Kennedy JL. Childhood aggression, callous-unemotional traits and oxytocin genes. *Eur Child Adolesc Psychiatry* 21: 125–132, 2012. doi:10.1007/s00787-012-0240-6.

69. Belin V, Moos F. Paired recordings from supraoptic and paraventricular oxytocin cells in suckled rats: recruitment and synchronization. *J Physiol* 377: 369–390, 1986. doi:10.1113/jphysiol.1986.sp016192.

70. Bell CJ, Nicholson H, Mulder RT, Luty SE, Joyce PR. Plasma oxytocin levels in depression and their correlation with the temperament dimension of reward dependence. *J Psychopharmacol* 20: 656–660, 2006. doi:10.1177/0269881106060512.

71. Bell WB. The pituitary body and the therapeutic value of the infundibular extract in shock, uterine atony, and intestinal paresis. *BMJ* 2: 1609–1613, 1909. doi:10.1136/bmj.2.2553.1609.

72. Belle MD, Hughes AT, Bechtold DA, Cunningham P, Pierucci M, Burdakov D, Piggins HD. Acute suppressive and long-term phase modulation actions of orexin on the mammalian circadian clock. *J Neurosci* 34: 3607–3621, 2014. doi:10.1523/JNEUROSCI.3388-13.2014.

73. Bendix M, Uvnäs-Moberg K, Petersson M, Gustavsson P, Svanborg P, Åsberg M, Jokinen J. Plasma oxytocin and personality traits in psychiatric outpatients. *Psychoneuroendocrinology* 57: 102–110, 2015. doi:10.1016/j.psyneuen.2015.04.003.

74. Benelli A, Bertolini A, Poggioli R, Menozzi B, Basaglia R, Arletti R. Polymodal dose-response curve for oxytocin in the social recognition test. *Neuropeptides* 28: 251–255, 1995. doi:10.1016/0143-4179(95)90029-2.

75. Bentzley BS, Jhou TC, Aston-Jones G. Economic demand predicts addiction-like behavior and therapeutic efficacy of oxytocin in the rat. *Proc Natl Acad Sci USA* 111: 11822–11827, 2014. doi:10.1073/pnas.1406324111.

76. Bernstein HG, Müller S, Dobrowolny H, Wolke C, Lendeckel U, Bukowska A, Keilhoff G, Becker A, Trübner K, Steiner J, Bogerts B. Insulin-regulated aminopeptidase immunoreactivity is abundantly present in human hypothalamus and posterior pituitary gland, with reduced expression in paraventricular and suprachiasmatic neurons in chronic schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 267: 427–443, 2017. doi:10.1007/s00406-016-0757-7.

77. Bertsch K, Gamer M, Schmidt B, Schmidinger I, Walther S, Kästel T, Schnell K, Büchel C, Domes G, Herpertz SC. Oxytocin and reduction of social threat hypersensitivity in women with borderline personality disorder. *Am J Psychiatry* 170: 1169–1177, 2013. doi:10.1176/appi.ajp.2013.13020263.

78. Bertsch K, Schmidinger I, Neumann ID, Herpertz SC. Reduced plasma oxytocin levels in female patients with borderline personality disorder. *Horm Behav* 63: 424–429, 2013. doi:10.1016/j.yhbeh.2012.11.013.

79. Beyer CE, Dwyer JM, Platt BJ, Neal S, Luo B, Ling HP, Lin Q, Mark RJ, Rosenzweig-Lipson S, Schechter LE. Angiotensin IV elevates oxytocin levels in the rat amygdala and produces anxiolytic-like activity through subsequent oxytocin receptor activation. *Psychopharmacology (Berl)* 209: 303–311, 2010. doi:10.1007/s00213-010-1791-1.

80. Bick J, Dozier M. Mothers' and children's concentrations of oxytocin following close, physical interactions with biological and non-biological children. *Dev Psychobiol* 52: 100–107, 2010. doi:10.1002/dev.20411.

81. Bicknell RJ, Leng G, Lincoln DW, Russell JA. Naloxone excites oxytocin neurones in the supraoptic nucleus of lactating rats after chronic morphine treatment. *J Physiol* 396: 297–317, 1988. doi:10.1113/jphysiol.1988.sp016963.

82. Bignante EA, Rodriguez Manzanares PA, Mlewski EC, Bertotto ME, Bussolino DF, Paglini G, Molina VA. Involvement of septal Cdk5 in the emergence of excessive anxiety induced by stress. *Eur Neuropsychopharmacol* 18: 578–588, 2008. doi:10.1016/j.euroneuro.2008.02.007.

83. Billings LB, Spero JA, Vollmer RR, Amico JA. Oxytocin null mice ingest enhanced amounts of sweet solutions during light and dark cycles and during repeated shaker stress. *Behav Brain Res* 171: 134–141, 2006. doi:10.1016/j.bbr.2006.03.028.

84. Black BL, Olson EN. Transcriptional control of muscle development by myocyte enhancer factor-2 (MEF2) proteins. *Annu Rev Cell Dev Biol* 14: 167–196, 1998. doi:10.1146/annurev.cellbio.14.1.167.

85. Blaicher W, Gruber D, Bieglmayer C, Blaicher AM, Knogler W, Huber JC. The role of oxytocin in relation to female sexual arousal. *Gynecol Obstet Invest* 47: 125–126, 1999. doi:10.1159/000010075.

86. Blandón-Gitlin I, Pezdek K, Saldivar S, Steelman E. Oxytocin eliminates the own-race bias in face recognition memory. *Brain Res* 1580: 180–187, 2014. doi:10.1016/j.brainres.2013.07.015.

87. Blanks AM, Shmygol A, Thornton S. Regulation of oxytocin receptors and oxytocin receptor signaling. *Semin Reprod Med* 25: 52–59, 2007. doi:10.1055/s-2006-956775.

88. Blevins JE, Eakin TJ, Murphy JA, Schwartz MW, Baskin DG. Oxytocin innervation of caudal brainstem nuclei activated by cholecystokinin. *Brain Res* 993: 30–41, 2003. doi:10.1016/j.brainres.2003.08.036.

89. Blume A, Bosch OJ, Miklos S, Torner L, Wales L, Waldherr M, Neumann ID. Oxytocin reduces anxiety via ERK1/2 activation: local effect within the rat hypothalamic paraventricular nucleus. *Eur J Neurosci* 27: 1947–1956, 2008. doi:10.1111/j.1460-9568.2008.06184.x.

90. Boccia ML, Goursaud AP, Bachevalier J, Anderson KD, Pedersen CA. Peripherally administered non-peptide oxytocin antagonist, L368,899, accumulates in limbic brain areas: a new pharmacological tool for the study of social motivation in non-human primates. *Horm Behav* 52: 344–351, 2007. doi:10.1016/j.yhbeh.2007.05.009.

91. Boccia ML, Panicker AK, Pedersen C, Petrusz P. Oxytocin receptors in non-human primate brain visualized with monoclonal antibody. *Neuroreport* 12: 1723–1726, 2001. doi:10.1097/00001756-200106130-00041.

92. Boccia ML, Petrusz P, Suzuki K, Marson L, Pedersen CA. Immunohistochemical localization of oxytocin receptors in human brain. *Neuroscience* 253: 155–164, 2013. doi:10.1016/j.neuroscience.2013.08.048.

93. Bohus B, De Wied D. Inhibitory and facilitatory effect of two related peptides on extinction of avoidance behavior. *Science* 153: 318–320, 1966. doi:10.1126/science.153.3733.318.

94. Bondy CA, Jensen RT, Brady LS, Gainer H. Cholecystokinin evokes secretion of oxytocin and vasopressin from rat neural lobe independent of external calcium. *Proc Natl Acad Sci USA* 86: 5198–5201, 1989. doi:10.1073/pnas.86.13.5198.

95. Bonefeld BE, Elfving B, Wegener G. Reference genes for normalization: a study of rat brain tissue. *Synapse* 62: 302–309, 2008. doi:10.1002/syn.20496.

96. Born J, Lange T, Kern W, McGregor GP, Bickel U, Fehm HL. Sniffing neuropeptides: a transnasal approach to the human brain. *Nat Neurosci* 5: 514–516, 2002. doi:10.1038/nn0602-849.

97. Borrow AP, Cameron NM. The role of oxytocin in mating and pregnancy. *Horm Behav* 61: 266–276, 2012. doi:10.1016/j.yhbeh.2011.11.001.

98. Borthwick AD, Liddle J, Davies DE, Exall AM, Hamlett C, Hickey DM, Mason AM, Smith IE, Nerozzi F, Peace S, Pollard D, Sollis SL, Allen MJ, Woollard PM, Pullen MA, Westfall TD, Stanislaus DJ. Pyridyl-2,5-diketopiperazines as potent, selective, and orally bioavailable oxytocin antagonists: synthesis, pharmacokinetics, and in vivo potency. *J Med Chem* 55: 783–796, 2012. doi:10.1021/jm201287w.

99. Bosch OJ. Maternal aggression in rodents: brain oxytocin and vasopressin mediate pup defence. *Philos Trans R Soc Lond B Biol Sci* 368: 20130085, 2013. doi:10.1098/rstb.2013.0085.

100. Bosch OJ, Dabrowska J, Modi ME, Johnson ZV, Keebaugh AC, Barrett CE, Ahern TH, Guo J, Grinevich V, Rainnie DG, Neumann ID, Young LJ. Oxytocin in the nucleus accumbens shell reverses CRFR2-evoked passive stress-coping after partner loss in monogamous male prairie voles. *Psychoneuroendocrinology* 64: 66–78, 2016. doi:10.1016/j.psyneuen.2015.11.011.

101. Bosch OJ, Krömer SA, Brunton PJ, Neumann ID. Release of oxytocin in the hypothalamic paraventricular nucleus, but not central amygdala or lateral septum in lactating residents and virgin intruders during maternal defence. *Neuroscience* 124: 439–448, 2004. doi:10.1016/j.neuroscience.2003.11.028.

102. Bosch OJ, Meddle SL, Beiderbeck DI, Douglas AJ, Neumann ID. Brain oxytocin correlates with maternal aggression: link to anxiety. *J Neurosci* 25: 6807–6815, 2005. doi:10.1523/JNEUROSCI.1342-05.2005.

103. Bosch OJ, Nair HP, Ahern TH, Neumann ID, Young LJ. The CRF system mediates increased passive stress-coping behavior following the loss of a bonded partner in a monogamous rodent. *Neuropsychopharmacology* 34: 1406–1415, 2009. doi:10.1038/npp.2008.154.

104. Bosch OJ, Neumann ID. Both oxytocin and vasopressin are mediators of maternal care and aggression in rodents: from central release to sites of action. *Horm Behav* 61: 293–303, 2012. doi:10.1016/j.yhbeh.2011.11.002.

105. Bosch OJ, Neumann ID. Brain vasopressin is an important regulator of maternal behavior independent of dams' trait anxiety. *Proc Natl Acad Sci USA* 105: 17139–17144, 2008. doi:10.1073/pnas.0807412105.

106. Bosch OJ, Neumann ID. Vasopressin released within the central amygdala promotes maternal aggression. *Eur J Neurosci* 31: 883–891, 2010. doi:10.1111/j.1460-9568.2010.07115.x.

107. Bosch OJ, Pförtsch J, Beiderbeck DI, Landgraf R, Neumann ID. Maternal behaviour is associated with vasopressin release in the medial preoptic area and bed nucleus of the stria terminalis in the rat. *J Neuroendocrinol* 22: 420–429, 2010. doi:10.1111/j.1365-2826.2010.01984.x.

108. Bowen MT, Neumann ID. The multidimensional therapeutic potential of targeting the brain oxytocin system for the treatment of substance use disorders. *Curr Top Behav Neurosci*. In press.

109. Bowen MT, Peters ST, Absalom N, Chebib M, Neumann ID, McGregor IS. Oxytocin prevents ethanol actions at δ subunit-containing GABAA receptors and attenuates ethanol-induced motor impairment in rats. *Proc Natl Acad Sci USA* 112: 3104–3109, 2015. doi:10.1073/pnas.1416900112.

110. Brambilla M, Manenti R, de Girolamo G, Adenzato M, Bocchio-Chiavetto L, Cotelli M. Effects of intranasal oxytocin on long-term memory in healthy humans: a systematic review. *Drug Dev Res* 77: 479–488, 2016. doi:10.1002/ddr.21343.

111. Brandt KJ, Carpintero R, Gruaz L, Molnarfi N, Burger D. A novel MEK2/PI3Kδ pathway controls the expression of IL-1 receptor antagonist in IFN-β-activated human monocytes. *J Leukoc Biol* 88: 1191–1200, 2010. doi:10.1189/jlb.0510312.

112. Brandtzaeg OK, Johnsen E, Roberg-Larsen H, Seip KF, MacLean EL, Gesquiere LR, Leknes S, Lundanes E, Wilson SR. Proteomics tools reveal startlingly high amounts of oxytocin in plasma and serum. *Sci Rep* 6: 31693, 2016. doi:10.1038/srep31693.

113. Bredewold R, Smith CJ, Dumais KM, Veenema AH. Sex-specific modulation of juvenile social play behavior by vasopressin and oxytocin depends on social context. *Front Behav Neurosci* 8: 216, 2014. doi:10.3389/fnbeh.2014.00216.

114. Breton C, Di Scala-Guenot D, Zingg HH. Oxytocin receptor gene expression in rat mammary gland: structural characterization and regulation. *J Mol Endocrinol* 27: 175–189, 2001. doi:10.1677/jme.0.0270175.

115. Breton C, Zingg HH. Expression and region-specific regulation of the oxytocin receptor gene in rat brain. *Endocrinology* 138: 1857–1862, 1997. doi:10.1210/endo.138.5.5127.

116. Breton JD, Poisbeau P, Darbon P. Antinociceptive action of oxytocin involves inhibition of potassium channel currents in lamina II neurons of the rat spinal cord. *Mol Pain* 5: 63, 2009. doi:10.1186/1744-8069-5-63.

117. Brett M, Baxendale S. Motherhood and memory: a review. *Psychoneuroendocrinology* 26: 339–362, 2001. doi:10.1016/S0306-4530(01)00003-8.

118. Bridges RS, DiBiase R, Loundes DD, Doherty PC. Prolactin stimulation of maternal behavior in female rats. *Science* 227: 782–784, 1985. doi:10.1126/science.3969568.

119. Brighton PJ, Rana S, Challiss RJ, Konje JC, Willets JM. Arrestins differentially regulate histamine- and oxytocin-evoked phospholipase C and mitogen-activated protein

kinase signalling in myometrial cells. *Br J Pharmacol* 162: 1603–1617, 2011. doi:10.1111/j.1476-5381.2010.01173.x.

120. Brinton RE, Wamsley JK, Gee KW, Wan YP, Yamamura HI. [3H]oxytocin binding sites in the rat brain demonstrated by quantitative light microscopic autoradiography. *Eur J Pharmacol* 102: 365–367, 1984. doi:10.1016/0014-2999(84)90270-X.

121. Brooks CM, Ishikawa T, Koizumi K, Lu HH. Activity of neurones in the paraventricular nucleus of the hypothalamus and its control. *J Physiol* 182: 217–231, 1966. doi:10.1113/jphysiol.1966.sp007820.

122. Brown CH, Munro G, Johnstone LE, Robson AC, Landgraf R, Russell JA. Oxytocin neurone autoexcitation during morphine withdrawal in anaesthetized rats. *Neuroreport* 8: 951–955, 1997. doi:10.1097/00001756-199703030-00027.

123. Brown CH, Russell JA, Leng G. Opioid modulation of magnocellular neurosecretory cell activity. *Neurosci Res* 36: 97–120, 2000. doi:10.1016/S0168-0102(99)00121-2.

124. Brownstein MJ, Russell JT, Gainer H. Synthesis, transport, and release of posterior pituitary hormones. *Science* 207: 373–378, 1980. doi:10.1126/science.6153132.

125. Bruins J, Hijman R, Van Ree JM. Effect of a single dose of des-glycinamide-[Arg8]vasopressin or oxytocin on cognitive processes in young healthy subjects. *Peptides* 13: 461–468, 1992. doi:10.1016/0196-9781(92)90075-E.

126. Brunton PJ, Russell JA. The expectant brain: adapting for motherhood. *Nat Rev Neurosci* 9: 11–25, 2008. doi:10.1038/nrn2280.

127. Buffone AE, Poulin MJ. Empathy, target distress, and neurohormone genes interact to predict aggression for others-even without provocation. *Pers Soc Psychol Bull* 40: 1406–1422, 2014. doi:10.1177/0146167214549320.

128. Buijs RM, Swaab DF, Dogterom J, van Leeuwen FW. Intra- and extrahypothalamic vasopressin and oxytocin pathways in the rat. Pathways to the limbic system, medulla oblongata and spinal cord. *Cell Tissue Res* 192: 423–435, 1978. doi:10.1007/BF00224932.

129. Buijs RM, Geffard M, Pool CW, Hoorneman EM. The dopaminergic innervation of the supraoptic and paraventricular nucleus. A light and electron microscopical study. *Brain Res* 323: 65–72, 1984. doi:10.1016/0006-8993(84)90265-8.

130. Buijs RM, Swaab DF. Immuno-electron microscopical demonstration of vasopressin and oxytocin synapses in the limbic system of the rat. *Cell Tissue Res* 204: 355–365, 1979. doi:10.1007/BF00233648.

131. Bülbül M, Babygirija R, Cerjak D, Yoshimoto S, Ludwig K, Takahashi T. Hypothalamic oxytocin attenuates CRF expression via GABA(A) receptors in rats. *Brain Res* 1387: 39–45, 2011. doi:10.1016/j.brainres.2011.02.091.

132. Burbach JP. Regulation of gene promoters of hypothalamic peptides. *Front Neuroendocrinol* 23: 342–369, 2002. doi:10.1016/S0091-3022(02)00005-5.

133. Burgermeister E, Chuderland D, Hanoch T, Meyer M, Liscovitch M, Seger R. Interaction with MEK causes nuclear export and downregulation of peroxisome proliferator-activated receptor gamma. *Mol Cell Biol* 27: 803–817, 2007. doi:10.1128/MCB.00601-06.

134. Burkett JP, Andari E, Johnson ZV, Curry DC, de Waal FB, Young LJ. Oxytocin-dependent consolation behavior in rodents. *Science* 351: 375–378, 2016. doi:10.1126/science.aac4785.

135. Burri A, Heinrichs M, Schedlowski M, Kruger TH. The acute effects of intranasal oxytocin administration on endocrine and sexual function in males. *Psychoneuroendocrinology* 33: 591–600, 2008. doi:10.1016/j.psyneuen.2008.01.014.

136. Buske-Kirschbaum A, Schmitt J, Plessow F, Romanos M, Weidinger S, Roessner V. Psychoendocrine and psychoneuroimmunological mechanisms in the comorbidity of atopic eczema and attention deficit/hyperactivity disorder. *Psychoneuroendocrinology* 38: 12–23, 2013. doi:10.1016/j.psyneuen.2012.09.017.

137. Busnelli M, Bulgheroni E, Manning M, Kleinau G, Chini B. Selective and potent agonists and antagonists for investigating the role of mouse oxytocin receptors. *J Pharmacol Exp Ther* 346: 318–327, 2013. doi:10.1124/jpet.113.202994.

138. Busnelli M, Kleinau G, Muttenthaler M, Stoev S, Manning M, Bibic L, Howell LA, McCormick PJ, Di Lascio S, Braida D, Sala M, Rovati GE, Bellini T, Chini B. Design and characterization of superpotent bivalent ligands targeting oxytocin receptor dimers via a channel-like structure. *J Med Chem* 59: 7152–7166, 2016. doi:10.1021/acs.jmedchem.6b00564.

139. Busnelli M, Peverelli E, Mantovani G, Spada A, Chini B. Deciphering the specific role of G(αi/o) isoforms: functional selective oxytocin ligands and somatostatin SST5 receptor mutants. *Biochem Soc Trans* 41: 166–171, 2013. doi:10.1042/BST20120306.

140. Busnelli M, Saulière A, Manning M, Bouvier M, Galés C, Chini B. Functional selective oxytocin-derived agonists discriminate between individual G protein family subtypes. *J Biol Chem* 287: 3617–3629, 2012. doi:10.1074/jbc.M111.277178.

141. Button KS, Ioannidis JP, Mokrysz C, Nosek BA, Flint J, Robinson ES, Munafò MR. Power failure: why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci* 14: 365–376, 2013. doi:10.1038/nrn3475.

142. Caffé AR, Van Ryen PC, Van der Woude TP, Van Leeuwen FW. Vasopressin and oxytocin systems in the brain and upper spinal cord of Macaca fascicularis. *J Comp Neurol* 287: 302–325, 1989. doi:10.1002/cne.902870304.

143. Calcagnoli F, de Boer SF, Althaus M, den Boer JA, Koolhaas JM. Antiaggressive activity of central oxytocin in male rats. *Psychopharmacology (Berl)* 229: 639–651, 2013. doi:10.1007/s00213-013-3124-7.

144. Calcagnoli F, de Boer SF, Beiderbeck DI, Althaus M, Koolhaas JM, Neumann ID. Local oxytocin expression and oxytocin receptor binding in the male rat brain is associated with aggressiveness. *Behav Brain Res* 261: 315–322, 2014. doi:10.1016/j.bbr.2013.12.050.

145. Calcagnoli F, Stubbendorff C, Meyer N, de Boer SF, Althaus M, Koolhaas JM. Oxytocin microinjected into the central amygdaloid nuclei exerts anti-aggressive effects in male rats. *Neuropharmacology* 90: 74–81, 2015. doi:10.1016/j.neuropharm.2014.11.012.

146. Caldwell JD, Jirikowski GF, Greer ER, Stumpf WE, Pedersen CA. Ovarian steroids and sexual interaction alter oxytocinergic content and distribution in the basal forebrain. *Brain Res* 446: 236–244, 1988. doi:10.1016/0006-8993(88)90882-7.

147. Cameron EZ, Setsaas TH, Linklater WL. Social bonds between unrelated females increase reproductive success in feral horses. *Proc Natl Acad Sci USA* 106: 13850–13853, 2009. doi:10.1073/pnas.0900639106.

148. Cameron N, Erskine MS. c-FOS expression in the forebrain after mating in the female rat is altered by adrenalectomy. *Neuroendocrinology* 77: 305–313, 2003. doi:10.1159/000070283.

149. Cammarota M, Bevilaqua LR, Vianna MR, Medina JH, Izquierdo I. The extinction of conditioned fear: structural and molecular basis and therapeutic use. *Rev Bras Psiquiatr* 29: 80–85, 2007. doi:10.1590/S1516-44462006005000022.

150. Campbell-Smith EJ, Holmes NM, Lingawi NW, Panayi MC, Westbrook RF. Oxytocin signaling in basolateral and central amygdala nuclei differentially regulates the acquisition, expression, and extinction of context-conditioned fear in rats. *Learn Mem* 22: 247–257, 2015. doi:10.1101/lm.036962.114.

151. Campbell A, Hausmann M. Effects of oxytocin on women's aggression depend on state anxiety. *Aggress Behav* 39: 316–322, 2013. doi:10.1002/ab.21478.

152. Campbell P, Ophir AG, Phelps SM. Central vasopressin and oxytocin receptor distributions in two species of singing mice. *J Comp Neurol* 516: 321–333, 2009. doi:10.1002/cne.22116.

153. Cannon R, Lubar J, Congedo M, Thornton K, Towler K, Hutchens T. The effects of neurofeedback training in the cognitive division of the anterior cingulate gyrus. *Int J Neurosci* 117: 337–357, 2007. doi:10.1080/00207450500514003.

154. Caquineau C, Douglas AJ, Leng G. Effects of cholecystokinin in the supraoptic nucleus and paraventricular nucleus are negatively modulated by leptin in 24-h fasted lean male rats. *J Neuroendocrinol* 22: 446–452, 2010. doi:10.1111/j.1365-2826.2010.01982.x.

155. Caquineau C, Leng G, Guan XM, Jiang M, Van der Ploeg L, Douglas AJ. Effects of alpha-melanocyte-stimulating hormone on magnocellular oxytocin neurones and their activation at intromission in male rats. *J Neuroendocrinol* 18: 685–691, 2006. doi:10.1111/j.1365-2826.2006.01465.x.

156. Cardoso C, Orlando MA, Brown CA, Ellenbogen MA. Oxytocin and enhancement of the positive valence of social affiliation memories: an autobiographical memory study. *Soc Neurosci* 9: 186–195, 2014. doi:10.1080/17470919.2013.873079.

157. Carmichael MS, Humbert R, Dixen J, Palmisano G, Greenleaf W, Davidson JM. Plasma oxytocin increases in the human sexual response. *J Clin Endocrinol Metab* 64: 27–31, 1987. doi:10.1210/jcem-64-1-27.

158. Carmichael MS, Warburton VL, Dixen J, Davidson JM. Relationships among cardiovascular, muscular, and oxytocin responses during human sexual activity. *Arch Sex Behav* 23: 59–79, 1994. doi:10.1007/BF01541618.

159. Carson DS, Berquist SW, Trujillo TH, Garner JP, Hannah SL, Hyde SA, Sumiyoshi RD, Jackson LP, Moss JK, Strehlow MC, Cheshier SH, Partap S, Hardan AY, Parker KJ. Cerebrospinal fluid and plasma oxytocin concentrations are positively correlated and negatively predict anxiety in children. *Mol Psychiatry* 20: 1085–1090, 2015. doi:10.1038/mp.2014.132.

160. Carson DS, Cornish JL, Guastella AJ, Hunt GE, McGregor IS. Oxytocin decreases methamphetamine self-administration, methamphetamine hyperactivity, and relapse to methamphetamine-seeking behaviour in rats. *Neuropharmacology* 58: 38–43, 2010. doi:10.1016/j.neuropharm.2009.06.018.

161. Carson DS, Guastella AJ, Taylor ER, McGregor IS. A brief history of oxytocin and its role in modulating psychostimulant effects. *J Psychopharmacol* 27: 231–247, 2013. doi:10.1177/0269881112473788.

163. Carter CS, Altemus M, Chrousos GP. Neuroendocrine and emotional changes in the post-partum period. *Prog Brain Res* 133: 241–249, 2001. doi:10.1016/S0079-6123(01)33018-2.

164. Carter CS, Williams JR, Witt DM, Insel TR. Oxytocin and social bonding. *Ann N Y Acad Sci* 652: 204–211, 1992. doi:10.1111/j.1749-6632.1992.tb34356.x.

165. Cattaneo MG, Chini B, Vicentini LM. Oxytocin stimulates migration and invasion in human endothelial cells. *Br J Pharmacol* 153: 728–736, 2008. doi:10.1038/sj.bjp.0707609.

166. Caughey SD, Klampfl SM, Bishop VR, Pfoertsch J, Neumann ID, Bosch OJ, Meddle SL. Changes in the intensity of maternal aggression and central oxytocin and vasopressin V1a receptors across the peripartum period in the rat. *J Neuroendocrinol* 23: 1113–1124, 2011. doi:10.1111/j.1365-2826.2011.02224.x.

167. Cerf-Ducastel B, Murphy C. fMRI activation in response to odorants orally delivered in aqueous solutions. *Chem Senses* 26: 625–637, 2001. doi:10.1093/chemse/26.6.625.

168. Chagnon YC, Potvin O, Hudon C, Préville M. DNA methylation and single nucleotide variants in the brain-derived neurotrophic factor (BDNF) and oxytocin receptor (OXTR) genes are associated with anxiety/depression in older women. *Front Genet* 6: 230, 2015. doi:10.3389/fgene.2015.00230.

169. Champagne F, Diorio J, Sharma S, Meaney MJ. Naturally occurring variations in maternal behavior in the rat are associated with differences in estrogen-inducible central oxytocin receptors. *Proc Natl Acad Sci USA* 98: 12736–12741, 2001. doi:10.1073/pnas.221224598.

170. Champagne FA, Chretien P, Stevenson CW, Zhang TY, Gratton A, Meaney MJ. Variations in nucleus accumbens dopamine associated with individual differences in maternal behavior in the rat. *J Neurosci* 24: 4113–4123, 2004. doi:10.1523/JNEUROSCI.5322-03.2004.

171. Chandaka GK, Wang L, Senogles S, Armstrong WE. Late pregnancy is a critical period for changes in phosphorylated mitogen-activated protein kinase/extracellular signal-regulated kinase 1/2 in oxytocin neurones. *J Neuroendocrinol* 28: 2016, 2016. doi:10.1111/jne.12398.

172. Chappell AR, Freeman SM, Lin YK, LaPrairie JL, Inoue K, Young LJ, Hayes LD. Distributions of oxytocin and vasopressin 1a receptors in the Taiwan vole and their role in social monogamy. *J Zool (1987)* 299: 106–115, 2016. doi:10.1111/jzo.12332.

173. Chard T, Boyd NR, Forsling ML, McNeilly AS, Landon J. The development of a radioimmunoassay for oxytocin: the extraction of oxytocin from plasma, and its measurement during parturition in human and goat blood. *J Endocrinol* 48: 223–234, 1970. doi:10.1677/joe.0.0480223.

174. Chaviaras S, Mak P, Ralph D, Krishnan L, Broadbear JH. Assessing the antidepressant-like effects of carbetocin, an oxytocin agonist, using a modification of the forced swimming test. *Psychopharmacology (Berl)* 210: 35–43, 2010. doi:10.1007/s00213-010-1815-x.

175. Chen FS, Kumsta R, von Dawans B, Monakhov M, Ebstein RP, Heinrichs M. Common oxytocin receptor gene (OXTR) polymorphism and social support interact to reduce stress in humans. *Proc Natl Acad Sci USA* 108: 19937–19942, 2011. doi:10.1073/pnas.1113079108.

176. Chen K, Chang LS. Oxytocinergic neurotransmission at the hippocampus in the central neural regulation of penile erection in the rat. *Urology* 58: 107–112, 2001. doi:10.1016/S0090-4295(01)01000-7.

177. Chen Y, Lyga J. Brain-skin connection: stress, inflammation and skin aging. *Inflamm Allergy Drug Targets* 13: 177–190, 2014. doi:10.2174/1871528113666140522104422.

178. Chevaleyre V, Dayanithi G, Moos FC, Desarmenien MG. Developmental regulation of a local positive autocontrol of supraoptic neurons. *J Neurosci* 20: 5813–5819, 2000.

179. Chini B, Manning M. Agonist selectivity in the oxytocin/vasopressin receptor family: new insights and challenges. *Biochem Soc Trans* 35: 737–741, 2007. doi:10.1042/BST0350737.

180. Chini B, Manning M, Guillon G. Affinity and efficacy of selective agonists and antagonists for vasopressin and oxytocin receptors: an "easy guide" to receptor pharmacology. *Prog Brain Res* 170: 513–517, 2008. doi:10.1016/S0079-6123(08)00438-X.

181. Chiodera P, Louis F, Legros JJ. Simultaneous radioimmunoassay for plasma arginine-vasopressin and oxytocin using DEAE Sephadex A 25 extraction. *J Endocrinol Invest* 7: 287–293, 1984. doi:10.1007/BF03351004.

182. Cho MM, DeVries AC, Williams JR, Carter CS. The effects of oxytocin and vasopressin on partner preferences in male and female prairie voles (*Microtus ochrogaster*). *Behav Neurosci* 113: 1071–1079, 1999. doi:10.1037/0735-7044.113.5.1071.

183. Choe HK, Reed MD, Benavidez N, Montgomery D, Soares N, Yim YS, Choi GB. Oxytocin mediates entrainment of sensory stimuli to social cues of opposing valence. *Neuron* 87: 152–163, 2015. doi:10.1016/j.neuron.2015.06.022.

184. Choi JW, Kang SM, Lee Y, Hong SH, Sanek NA, Young WS, Lee HJ. MicroRNA profiling in the mouse hypothalamus reveals oxytocin-regulating microRNA. *J Neurochem* 126: 331–337, 2013. doi:10.1111/jnc.12308.

185. Choleris E, Devidze N, Kavaliers M, Pfaff DW. Steroidal/neuropeptide interactions in hypothalamus and amygdala related to social anxiety. *Prog Brain Res* 170: 291–303, 2008. doi:10.1016/S0079-6123(08)00424-X.

186. Choleris E, Gustafsson JA, Korach KS, Muglia LJ, Pfaff DW, Ogawa S. An estrogen-dependent four-gene micronet regulating social recognition: a study with oxytocin and estrogen receptor-alpha and -beta knockout mice. *Proc Natl Acad Sci USA* 100: 6192–6197, 2003. doi:10.1073/pnas.0631699100.

187. Chu K, Zingg HH. Activation of the mouse oxytocin promoter by the orphan receptor RORalpha. *J Mol Endocrinol* 23: 337–346, 1999. doi:10.1677/jme.0.0230337.

188. Chung D, Kim YS, Phillips JN, Ulloa A, Ku CY, Galan HL, Sanborn BM. Attenuation of canonical transient receptor potential-like channel 6 expression specifically reduces the diacylglycerol-mediated increase in intracellular calcium in human myometrial cells. *Endocrinology* 151: 406–416, 2010. doi:10.1210/en.2009-0085.

189. Cicutti NJ, Smyth CE, Rosaeg OP, Wilkinson M. Oxytocin receptor binding in rat and human heart. *Can J Cardiol* 15: 1267–1273, 1999.

190. Clark K, MacKenzie KF, Petkevicius K, Kristariyanto Y, Zhang J, Choi HG, Peggie M, Plater L, Pedrioli PG, McIver E, Gray NS, Arthur JS, Cohen P. Phosphorylation of CRTC3 by the salt-inducible kinases controls the interconversion of classically activated and regulatory macrophages. *Proc Natl Acad Sci USA* 109: 16986–16991, 2012. doi:10.1073/pnas.1215450109.

191. Clément P, Bernabé J, Compagnie S, Alexandre L, McCallum S, Giuliano F. Inhibition of ejaculation by the non-peptide oxytocin receptor antagonist GSK557296: a multilevel site of action. *Br J Pharmacol* 169: 1477–1485, 2013. doi:10.1111/bph.12198.

192. Clément P, Peeters M, Bernabé J, Denys P, Alexandre L, Giuliano F. Brain oxytocin receptors mediate ejaculation elicited by 7-hydroxy-2-(di-N-propylamino) tetralin (7-OH-DPAT) in anaesthetized rats. *Br J Pharmacol* 154: 1150–1159, 2008. doi:10.1038/bjp.2008.176.

193. Clipperton-Allen AE, Chen Y, Page DT. Autism-relevant behaviors are minimally impacted by conditional deletion of Pten in oxytocinergic neurons. *Autism Res* 9: 1248–1262, 2016. doi:10.1002/aur.1641.

194. Clipperton-Allen AE, Lee AW, Reyes A, Devidze N, Phan A, Pfaff DW, Choleris E. Oxytocin, vasopressin and estrogen receptor gene expression in relation to social

recognition in female mice. *Physiol Behav* 105: 915–924, 2012. doi:10.1016/j.physbeh.2011.10.025.

195. Cochran DM, Fallon D, Hill M, Frazier JA. The role of oxytocin in psychiatric disorders: a review of biological and therapeutic research findings. *Harv Rev Psychiatry* 21: 219–247, 2013. doi:10.1097/HRP.0b013e3182a75b7d.

196. Cohen H, Kaplan Z, Kozlovsky N, Gidron Y, Matar MA, Zohar J. Hippocampal microinfusion of oxytocin attenuates the behavioural response to stress by means of dynamic interplay with the glucocorticoid-catecholamine responses. *J Neuroendocrinol* 22: 889–904, 2010.

197. Colaianni G, Tamma R, Di Benedetto A, Yuen T, Sun L, Zaidi M, Zallone A. The oxytocin-bone axis. *J Neuroendocrinol* 26: 53–57, 2014. doi:10.1111/jne.12120.

198. Colucci S, Colaianni G, Mori G, Grano M, Zallone A. Human osteoclasts express oxytocin receptor. *Biochem Biophys Res Commun* 297: 442–445, 2002. doi:10.1016/S0006-291X(02)02009-0.

199. Consiglio AR, Borsoi A, Pereira GA, Lucion AB. Effects of oxytocin microinjected into the central amygdaloid nucleus and bed nucleus of stria terminalis on maternal aggressive behavior in rats. *Physiol Behav* 85: 354–362, 2005. doi:10.1016/j.physbeh.2005.05.002.

200. Consiglio AR, Lucion AB. Lesion of hypothalamic paraventricular nucleus and maternal aggressive behavior in female rats. *Physiol Behav* 59: 591–596, 1996. doi:10.1016/0031-9384(95)02117-5.

201. Conti F, Sertic S, Reversi A, Chini B. Intracellular trafficking of the human oxytocin receptor: evidence of receptor recycling via a Rab4/Rab5 "short cycle". *Am J Physiol Endocrinol Metab* 296: E532–E542, 2009. doi:10.1152/ajpendo.90590.2008.

202. Cook CJ, Devine CE. Antibody-based electrodes for hormonal and neurotransmitter measurements in vivo. *Electroanalysis* 10: 1108–1111, 1998. doi:10.1002/(SICI)1521-4109(199811)10:16<1108::AID-ELAN1108>3.0.CO;2-1.

203. Cook JR, MacIntyre DA, Samara E, Kim SH, Singh N, Johnson MR, Bennett PR, Terzidou V. Exogenous oxytocin modulates human myometrial microRNAs. *Am J Obstet Gynecol* 213: 65.e1–9, 2015. doi:10.1016/j.ajog.2015.03.015.

204. Corona G, Jannini EA, Vignozzi L, Rastrelli G, Maggi M. The hormonal control of ejaculation. *Nat Rev Urol* 9: 508–519, 2012. doi:10.1038/nrurol.2012.147.

205. Cort N, Einarsson S, Aström G. Effect of oxytocin and its long-acting analog on milk let-down and intramammary pressure in healthy lactating sows. *Am J Vet Res* 43: 1283–1285, 1982.

206. Cort N, Einarsson S, Viring S. Actions of oxytocin and a long-acting carba oxytocin analog on the porcine myometrium in vitro and in vivo. *Am J Vet Res* 40: 430–432, 1979.

207. Costa B, Pini S, Gabelloni P, Abelli M, Lari L, Cardini A, Muti M, Gesi C, Landi S, Galderisi S, Mucci A, Lucacchini A, Cassano GB, Martini C. Oxytocin receptor polymorphisms and adult attachment style in patients with depression. *Psychoneuroendocrinology* 34: 1506–1514, 2009. doi:10.1016/j.psyneuen.2009.05.006.

208. Cox BM, Young AB, See RE, Reichel CM. Sex differences in methamphetamine seeking in rats: impact of oxytocin. *Psychoneuroendocrinology* 38: 2343–2353, 2013. doi:10.1016/j.psyneuen.2013.05.005.

209. Cragg B, Ji G, Neugebauer V. Differential contributions of vasopressin V1A and oxytocin receptors in the amygdala to pain-related behaviors in rats. *Mol Pain* 12: 1744806916676491, 2016. doi:10.1177/1744806916676491.

210. Crawley JN, Chen T, Puri A, Washburn R, Sullivan TL, Hill JM, Young NB, Nadler JJ, Moy SS, Young LJ, Caldwell HK, Young WS. Social approach behaviors in oxytocin knockout mice: comparison of two independent lines tested in different laboratory environments. *Neuropeptides* 41: 145–163, 2007. doi:10.1016/j.npep.2007.02.002.

211. Crick FH. Thinking about the brain. *Sci Am* 241: 219–232, 1979. doi:10.1038/scientificamerican0979-219.

212. Crockford C, Wittig RM, Langergraber K, Ziegler TE, Zuberbühler K, Deschner T. Urinary oxytocin and social bonding in related and unrelated wild chimpanzees. *Proc Biol Sci* 280: 20122765, 2013. doi:10.1098/rspb.2012.2765.

213. Cross BA, Harris GW. Milk ejection following electrical stimulation of the pituitary stalk in rabbits. *Nature* 166: 994–995, 1950. doi:10.1038/166994b0.

214. Cross BA, Harris GW. The role of the neurohypophysis in the milk-ejection reflex. *J Endocrinol* 8: 148–161, 1952. doi:10.1677/joe.0.0080148.

215. Cryan JF, Markou A, Lucki I. Assessing antidepressant activity in rodents: recent developments and future needs. *Trends Pharmacol Sci* 23: 238–245, 2002. doi:10.1016/S0165-6147(02)02017-5.

216. Cryan JF, Slattery DA. Animal models of mood disorders: Recent developments. *Curr Opin Psychiatry* 20: 1–7, 2007. doi:10.1097/YCO.0b013e3280117733.

217. Cumbers MR, Chung ST, Wakerley JB. A neuromodulatory role for oxytocin within the supramammillary nucleus. *Neuropeptides* 41: 217–226, 2007. doi:10.1016/j.npep.2007.04.004.

218. Cyranowski JM, Hofkens TL, Frank E, Seltman H, Cai HM, Amico JA. Evidence of dysregulated peripheral oxytocin release among depressed women. *Psychosom Med* 70: 967–975, 2008. doi:10.1097/PSY.0b013e318188ade4.

219. Da Costa AP, Guevara-Guzman RG, Ohkura S, Goode JA, Kendrick KM. The role of oxytocin release in the paraventricular nucleus in the control of maternal behaviour in the sheep. *J Neuroendocrinol* 8: 163–177, 1996. doi:10.1046/j.1365-2826.1996.04411.x.

220. Dabrowska J, Hazra R, Ahern TH, Guo JD, McDonald AJ, Mascagni F, Muller JF, Young LJ, Rainnie DG. Neuroanatomical evidence for reciprocal regulation of the corticotrophin-releasing factor and oxytocin systems in the hypothalamus and the bed nucleus of the stria terminalis of the rat: implications for balancing stress and affect. *Psychoneuroendocrinology* 36: 1312–1326, 2011. doi:10.1016/j.psyneuen.2011.03.003.

221. Dabrowska J, Hazra R, Guo JD, Dewitt S, Rainnie DG. Central CRF neurons are not created equal: phenotypic differences in CRF-containing neurons of the rat paraventricular hypothalamus and the bed nucleus of the stria terminalis. *Front Neurosci* 7: 156, 2013. doi:10.3389/fnins.2013.00156.

222. Dadds MR, Moul C, Cauchi A, Dobson-Stone C, Hawes DJ, Brennan J, Ebstein RE. Methylation of the oxytocin receptor gene and oxytocin blood levels in the development of psychopathy. *Dev Psychopathol* 26: 33–40, 2014. doi:10.1017/S0954579413000497.

223. Dadds MR, Moul C, Cauchi A, Dobson-Stone C, Hawes DJ, Brennan J, Urwin R, Ebstein RE. Polymorphisms in the oxytocin receptor gene are associated with the development of psychopathy. *Dev Psychopathol* 26: 21–31, 2014. doi:10.1017/S0954579413000485.

224. Dade LA, Zatorre RJ, Jones-Gotman M. Olfactory learning: convergent findings from lesion and brain imaging studies in humans. *Brain* 125: 86–101, 2002. doi:10.1093/brain/awf003.

225. Dahlström A, Fuxe K. Localization of monoamines in the lower brain stem. *Experientia* 20: 398–399, 1964. doi:10.1007/BF02147990.

226. Dal Monte O, Noble PL, Turchi J, Cummins A, Averbeck BB. CSF and blood oxytocin concentration changes following intranasal delivery in macaque. *PLoS One* 9: e103677, 2014. doi:10.1371/journal.pone.0103677.

227. Dale HH. On some physiological actions of ergot. *J Physiol* 34: 163–206, 1906. doi:10.1113/jphysiol.1906.sp001148.

228. Dantzer R, Bluthe RM, Koob GF, Le Moal M. Modulation of social memory in male rats by neurohypophyseal peptides. *Psychopharmacology (Berl)* 91: 363–368, 1987. doi:10.1007/BF00518192.

229. Darlington DN, Keil LC, Dallman MF. Potentiation of hormonal responses to hemorrhage and fasting, but not hypoglycemia in conscious adrenalectomized rats. *Endocrinology* 125: 1398–1406, 1989. doi:10.1210/endo-125-3-1398.

230. Dawood MY, Raghavan KS, Pociask C. Radioimmunoassay of oxytocin. *J Endocrinol* 76: 261–270, 1978. doi:10.1677/joe.0.0760261.

231. Day NC, Hall MD, Hughes J. Modulation of hypothalamic cholecystokinin receptor density with changes in magnocellular activity: a quantitative autoradiographic study. *Neuroscience* 29: 371–383, 1989. doi:10.1016/0306-4522(89)90064-X.

232. De-Miguel FF, Trueta C. Synaptic and extrasynaptic secretion of serotonin. *Cell Mol Neurobiol* 25: 297–312, 2005. doi:10.1007/s10571-005-3061-z.

233. De Dreu CK, Greer LL, Handgraaf MJ, Shalvi S, Van Kleef GA. Oxytocin modulates selection of allies in intergroup conflict. *Proc Biol Sci* 279: 1150–1154, 2012. doi:10.1098/rspb.2011.1444.

234. De Dreu CK, Greer LL, Handgraaf MJ, Shalvi S, Van Kleef GA, Baas M, Ten Velden FS, Van Dijk E, Feith SW. The neuropeptide oxytocin regulates parochial altruism in intergroup conflict among humans. *Science* 328: 1408–1411, 2010. doi:10.1126/science.1189047.

235. De Dreu CK, Kret ME. Oxytocin conditions intergroup relations through upregulated in-group empathy, cooperation, conformity, and defense. *Biol Psychiatry* 79: 165–173, 2016. doi:10.1016/j.biopsych.2015.03.020.

236. de Jong TR, Beiderbeck DI, Neumann ID. Measuring virgin female aggression in the female intruder test (FIT): effects of oxytocin, estrous cycle, and anxiety. *PLoS One* 9: e91701, 2014. doi:10.1371/journal.pone.0091701.

237. Jong TR, Menon R, Bludau A, Grund T, Biermeier V, Klampfl SM, Jurek B, Bosch OJ, Hellhammer J, Neumann ID. Salivary oxytocin concentrations in response to running, sexual self-stimulation, breastfeeding and the TSST: The Regensburg Oxytocin Challenge (ROC) study. *Psychoneuroendocrinology* 62: 381–388, 2015. doi:10.1016/j.psyneuen.2015.08.027.

238. de Jong TR, Neumann ID. Oxytocin and Aggression. *Curr Top Behav Neurosci*. In press. doi:10.1007/7854_2017_13.

239. de Jong TR, Veening JG, Olivier B, Waldinger MD. Oxytocin involvement in SSRI-induced delayed ejaculation: a review of animal studies. *J Sex Med* 4: 14–28, 2007. doi:10.1111/j.1743-6109.2006.00394.x.

240. de Kock CP, Wierda KD, Bosman LW, Min R, Koksma JJ, Mansvelder HD, Verhage M, Brussaard AB. Somatodendritic secretion in oxytocin neurons is upregulated during the female reproductive cycle. *J Neurosci* 23: 2726–2734, 2003.

241. de la Mora MP, Pérez-Carrera D, Crespo-Ramírez M, Tarakanov A, Fuxe K, Borroto-Escuela DO. Signaling in dopamine D2 receptor-oxytocin receptor heterocomplexes and its relevance for the anxiolytic effects of dopamine and oxytocin interactions in the amygdala of the rat. *Biochim Biophys Acta* 1862: 2075–2085, 2016. doi:10.1016/j.bbadis.2016.07.004.

242. de Oliveira DC, Zuardi AW, Graeff FG, Queiroz RH, Crippa JA. Anxiolytic-like effect of oxytocin in the simulated public speaking test. *J Psychopharmacol* 26: 497–504, 2012. doi:10.1177/0269881111400642.

243. DeVries AC, Young WS III, Nelson RJ. Reduced aggressive behaviour in mice with targeted disruption of the oxytocin gene. *J Neuroendocrinol* 9: 363–368, 1997. doi:10.1046/j.1365-2826.1997.t01-1-00589.x.

244. De Vries GJ, Buijs RM. The origin of the vasopressinergic and oxytocinergic innervation of the rat brain with special reference to the lateral septum. *Brain Res* 273: 307–317, 1983. doi:10.1016/0006-8993(83)90855-7.

245. de Waal FB. The antiquity of empathy. *Science* 336: 874–876, 2012. doi:10.1126/science.1220999.

246. de Weerth C, Buitelaar JK. Physiological stress reactivity in human pregnancy–a review. *Neurosci Biobehav Rev* 29: 295–312, 2005. doi:10.1016/j.neubiorev.2004.10.005.

247. De Wied D. The influence of the posterior and intermediate lobe of the pituitary and pituitary peptides on the maintenance of a conditioned avoidance response in rats. *Int J Neuropharmacol* 4: 157–167, 1965. doi:10.1016/0028-3908(65)90005-5.

248. De Wied D. Long term effect of vasopressin on the maintenance of a conditioned avoidance response in rats. *Nature* 232: 58–60, 1971. doi:10.1038/232058a0.

249. Deblon N, Veyrat-Durebex C, Bourgoin L, Caillon A, Bussier AL, Petrosino S, Piscitelli F, Legros JJ, Geenen V, Foti M, Wahli W, Di Marzo V, Rohner-Jeanrenaud F. Mechanisms of the anti-obesity effects of oxytocin in diet-induced obese rats. *PLoS One* 6: e25565, 2011. doi:10.1371/journal.pone.0025565.

250. Deing V, Roggenkamp D, Kühnl J, Gruschka A, Stäb F, Wenck H, Bürkle A, Neufang G. Oxytocin modulates proliferation and stress responses of human skin cells: implications for atopic dermatitis. *Exp Dermatol* 22: 399–405, 2013. doi:10.1111/exd.12155.

251. Deisseroth K. Optogenetics. *Nat Methods* 8: 26–29, 2011. doi:10.1038/nmeth.f.324.

252. Demirci E, Ozmen S, Kilic E, Oztop DB. The relationship between aggression, empathy skills and serum oxytocin levels in male children and adolescents with attention deficit and hyperactivity disorder. *Behav Pharmacol* 27: 681–688, 2016. doi:10.1097/FBP.0000000000000234.

253. Demitrack MA, Gold PW. Oxytocin: neurobiologic considerations and their implications for affective illness. *Prog Neuropsychopharmacol Biol Psychiatry* 12, Suppl: S23–S51, 1988. doi:10.1016/0278-5846(88)90072-3.

254. Déry MC, Chaudhry P, Leblanc V, Parent S, Fortier AM, Asselin E. Oxytocin increases invasive properties of endometrial cancer cells through phosphatidylinositol 3-kinase/AKT-dependent up-regulation of cyclooxygenase-1, -2, and X-linked inhibitor of apoptosis protein. *Biol Reprod* 85: 1133–1142, 2011. doi:10.1095/biolreprod.111.093278.

255. Desbonnet L, Clarke G, Traplin A, O'Sullivan O, Crispie F, Moloney RD, Cotter PD, Dinan TG, Cryan JF. Gut microbiota depletion from early adolescence in mice: Implications for brain and behaviour. *Brain Behav Immun* 48: 165–173, 2015. doi:10.1016/j.bbi.2015.04.004.

256. Detillion CE, Craft TK, Glasper ER, Prendergast BJ, DeVries AC. Social facilitation of wound healing. *Psychoneuroendocrinology* 29: 1004–1011, 2004. doi:10.1016/j.psyneuen.2003.10.003.

257. Devanand D, Lo E, Sackeim H, Ross F, Halbreich U, Prudic J, Cooper T. Specificity of ECT treatment parameters on plasma vasopressin and oxytocin. In: *Annual Meeting of the Society for Biological Psychiatry, Montreal, Canada*. Montreal, Canada: Society for Biological Psychiatry, 1988.

258. Devanand DP, Lisanby S, Lo ES, Fitzsimons L, Cooper TB, Halbreich U, Sackeim HA. Effects of electroconvulsive therapy on plasma vasopressin and oxytocin. *Biol Psychiatry* 44: 610–616, 1998. doi:10.1016/S0006-3223(98)00086-9.

259. Devidze N, Mong JA, Jasnow AM, Kow LM, Pfaff DW. Sex and estrogenic effects on coexpression of mRNAs in single ventromedial hypothalamic neurons. *Proc Natl Acad Sci USA* 102: 14446–14451, 2005. doi:10.1073/pnas.0507144102.

260. Devost D, Carrier ME, Zingg HH. Oxytocin-induced activation of eukaryotic elongation factor 2 in myometrial cells is mediated by protein kinase C. *Endocrinology* 149: 131–138, 2008. doi:10.1210/en.2007-0548.

261. Devost D, Wrzal P, Zingg HH. Oxytocin receptor signalling. *Prog Brain Res* 170: 167–176, 2008. doi:10.1016/S0079-6123(08)00415-9.

262. Dhakar MB, Rich ME, Reno EL, Lee HJ, Caldwell HK. Heightened aggressive behavior in mice with lifelong versus postweaning knockout of the oxytocin receptor. *Horm Behav* 62: 86–92, 2012. doi:10.1016/j.yhbeh.2012.05.007.

263. Dhuria SV, Hanson LR, Frey WH II. Intranasal delivery to the central nervous system: mechanisms and experimental considerations. *J Pharm Sci* 99: 1654–1673, 2010. doi:10.1002/jps.21924.

264. Di Benedetto A, Sun L, Zambonin CG, Tamma R, Nico B, Calvano CD, Colaianni G, Ji Y, Mori G, Grano M, Lu P, Colucci S, Yuen T, New MI, Zallone A, Zaidi M. Osteoblast regulation via ligand-activated nuclear trafficking of the oxytocin receptor. *Proc Natl Acad Sci USA* 111: 16502–16507, 2014. doi:10.1073/pnas.1419349111.

265. Di S, Malcher-Lopes R, Marcheselli VL, Bazan NG, Tasker JG. Rapid glucocorticoid-mediated endocannabinoid release and opposing regulation of glutamate and gamma-aminobutyric acid inputs to hypothalamic magnocellular neurons. *Endocrinology* 146: 4292–4301, 2005. doi:10.1210/en.2005-0610.

266. Di Scala-Guenot D, Mouginot D, Strosser MT. Increase of intracellular calcium induced by oxytocin in hypothalamic cultured astrocytes. *Glia* 11: 269–276, 1994. doi:10.1002/glia.440110308.

267. Di Simplicio M, Massey-Chase R, Cowen PJ, Harmer CJ. Oxytocin enhances processing of positive versus negative emotional information in healthy male volunteers. *J Psychopharmacol* 23: 241–248, 2009. doi:10.1177/0269881108095705.

268. Dietrich JB. The MEF2 family and the brain: from molecules to memory. *Cell Tissue Res* 352: 179–190, 2013. doi:10.1007/s00441-013-1565-2.

269. Ditzen B, Schaer M, Gabriel B, Bodenmann G, Ehlert U, Heinrichs M. Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. *Biol Psychiatry* 65: 728–731, 2009. doi:10.1016/j.biopsych.2008.10.011.

270. Dluzen DE, Muraoka S, Engelmann M, Ebner K, Landgraf R. Oxytocin induces preservation of social recognition in male rats by activating alpha-adrenoceptors of the olfactory bulb. *Eur J Neurosci* 12: 760–766, 2000. doi:10.1046/j.1460-9568.2000.00952.x.

271. Dluzen DE, Muraoka S, Engelmann M, Landgraf R. The effects of infusion of arginine vasopressin, oxytocin, or their antagonists into the olfactory bulb upon social recog-

nition responses in male rats. *Peptides* 19: 999–1005, 1998. doi:10.1016/S0196-9781(98)00047-3.

272. Dluzen DE, Muraoka S, Landgraf R. Olfactory bulb norepinephrine depletion abolishes vasopressin and oxytocin preservation of social recognition responses in rats. *Neurosci Lett* 254: 161–164, 1998. doi:10.1016/S0304-3940(98)00691-0.

273. Dodhia S, Hosanagar A, Fitzgerald DA, Labuschagne I, Wood AG, Nathan PJ, Phan KL. Modulation of resting-state amygdala-frontal functional connectivity by oxytocin in generalized social anxiety disorder. *Neuropsychopharmacology* 39: 2061–2069, 2014. doi:10.1038/npp.2014.53.

274. Dölen G, Darvishzadeh A, Huang KW, Malenka RC. Social reward requires coordinated activity of nucleus accumbens oxytocin and serotonin. *Nature* 501: 179–184, 2013. doi:10.1038/nature12518.

275. Dombret C, Nguyen T, Schakman O, Michaud JL, Hardin-Pouzet H, Bertrand MJ, De Backer O. Loss of Maged1 results in obesity, deficits of social interactions, impaired sexual behavior and severe alteration of mature oxytocin production in the hypothalamus. *Hum Mol Genet* 21: 4703–4717, 2012. doi:10.1093/hmg/dds310.

276. Domes G, Heinrichs M, Gläscher J, Büchel C, Braus DF, Herpertz SC. Oxytocin attenuates amygdala responses to emotional faces regardless of valence. *Biol Psychiatry* 62: 1187–1190, 2007. doi:10.1016/j.biopsych.2007.03.025.

277. Domes G, Lischke A, Berger C, Grossmann A, Hauenstein K, Heinrichs M, Herpertz SC. Effects of intranasal oxytocin on emotional face processing in women. *Psychoneuroendocrinology* 35: 83–93, 2010. doi:10.1016/j.psyneuen.2009.06.016.

278. Domes G, Normann C, Heinrichs M. The effect of oxytocin on attention to angry and happy faces in chronic depression. *BMC Psychiatry* 16: 92, 2016. doi:10.1186/s12888-016-0794-9.

279. Dominguez JM, Hull EM. Serotonin impairs copulation and attenuates ejaculation-induced glutamate activity in the medial preoptic area. *Behav Neurosci* 124: 554–557, 2010. doi:10.1037/a0020353.

280. Donaldson ZR, Young LJ. Oxytocin, vasopressin, and the neurogenetics of sociality. *Science* 322: 900–904, 2008. doi:10.1126/science.1158668.

281. Donner N, Neumann ID. Effects of chronic intracerebral prolactin on the oxytocinergic and vasopressinergic system of virgin ovariectomized rats. *Neuroendocrinology* 90: 315–322, 2009. doi:10.1159/000225986.

282. Douglas AJ, Brunton PJ, Bosch OJ, Russell JA, Neumann ID. Neuroendocrine responses to stress in mice: hyporesponsiveness in pregnancy and parturition. *Endocrinology* 144: 5268–5276, 2003. doi:10.1210/en.2003-0461.

283. Douglas AJ, Johnstone HA, Wigger A, Landgraf R, Russell JA, Neumann ID. The role of endogenous opioids in neurohypophysial and hypothalamo-pituitary-adrenal axis hormone secretory responses to stress in pregnant rats. *J Endocrinol* 158: 285–293, 1998. doi:10.1677/joe.0.1580285.

284. Douglas AJ, Leng G, Russell JA. The importance of oxytocin mechanisms in the control of mouse parturition. *Reproduction* 123: 543–552, 2002. doi:10.1530/rep.0.1230543.

285. Douglas AJ, Neumann I, Meeren HK, Leng G, Johnstone LE, Munro G, Russell JA. Central endogenous opioid inhibition of supraoptic oxytocin neurons in pregnant rats. *J Neurosci* 15: 5049–5057, 1995.

286. Drago F, Lissandrello CO. The "low-dose" concept and the paradoxical effects of prolactin on grooming and sexual behavior. *Eur J Pharmacol* 405: 131–137, 2000. doi:10.1016/S0014-2999(00)00678-6.

287. Dreifuss JJ, Tribollet E, Dubois-Dauphin M, Raggenbass M. Receptors and neural effects of oxytocin in the rodent hypothalamus and preoptic region. *Ciba Found Symp* 168: 187–199, 1992.

288. Du Vigneaud V, Ressler C, Swan J, Roberts CW, Katsoyannis PG, Gordon S. The synthesis of an octapeptide amide with the hormonal activity of oxytocin. *J Am Chem Soc* 75: 4879–4880, 1953. doi:10.1021/ja01115a553.

289. du Vigneaud V, Ressler C, Swan JM, Roberts CW, Katsoyannis PG. The Synthesis of Oxytocin1. *J Am Chem Soc* 76: 3115–3121, 1954. doi:10.1021/ja01641a004.

290. Du Vigneaud V, Ressler C, Trippett S. The sequence of amino acids in oxytocin, with a proposal for the structure of oxytocin. *J Biol Chem* 205: 949–957, 1953.

291. Dubois-Dauphin M, Pévet P, Barberis C, Tribollet E, Dreifuss JJ. Localization of binding sites for oxytocin in the brain of the golden hamster. *Neuroreport* 3: 797–800, 1992. doi:10.1097/00001756-199209000-00019.

292. Dubois-Dauphin M, Raggenbass M, Widmer H, Tribollet E, Dreifuss JJ. Morphological and electrophysiological evidence for postsynaptic localization of functional oxytocin receptors in the rat dorsal motor nucleus of the vagus nerve. *Brain Res* 575: 124–131, 1992. doi:10.1016/0006-8993(92)90431-8.

293. Duchemin A, Seelke AM, Simmons TC, Freeman SM, Bales KL. Localization of oxytocin receptors in the prairie vole (Microtus ochrogaster) neocortex. *Neuroscience* 348: 201–211, 2017. doi:10.1016/j.neuroscience.2017.02.017.

294. Dumais KM, Bredewold R, Mayer TE, Veenema AH. Sex differences in oxytocin receptor binding in forebrain regions: correlations with social interest in brain region- and sex- specific ways. *Horm Behav* 64: 693–701, 2013. doi:10.1016/j.yhbeh.2013.08.012.

295. Dunbar RI, Shultz S. Evolution in the social brain. *Science* 317: 1344–1347, 2007. doi:10.1126/science.1145463.

296. Dyball REJ, Koizumi K. Electrical activity in the supraoptic and paraventricular nuclei associated with neurohypophysial hormone release. *J Physiol* 201: 711–722, 1969. doi:10.1113/jphysiol.1969.sp008783.

297. Ebner K, Bosch OJ, Krömer SA, Singewald N, Neumann ID. Release of oxytocin in the rat central amygdala modulates stress-coping behavior and the release of excitatory amino acids. *Neuropsychopharmacology* 30: 223–230, 2005. doi:10.1038/sj.npp.1300607.

298. Ebner K, Wotjak CT, Landgraf R, Engelmann M. A single social defeat experience selectively stimulates the release of oxytocin, but not vasopressin, within the septal brain area of male rats. *Brain Res* 872: 87–92, 2000. doi:10.1016/S0006-8993(00)02464-1.

299. Eckertova M, Ondrejcakova M, Krskova K, Zorad S, Jezova D. Subchronic treatment of rats with oxytocin results in improved adipocyte differentiation and increased gene expression of factors involved in adipogenesis. *Br J Pharmacol* 162: 452–463, 2011. doi:10.1111/j.1476-5381.2010.01037.x.

300. Eckstein M, Becker B, Scheele D, Scholz C, Preckel K, Schlaepfer TE, Grinevich V, Kendrick KM, Maier W, Hurlemann R. Oxytocin facilitates the extinction of conditioned fear in humans. *Biol Psychiatry* 78: 194–202, 2015. doi:10.1016/j.biopsych.2014.10.015.

301. Eckstein M, Scheele D, Patin A, Preckel K, Becker B, Walter A, Domschke K, Grinevich V, Maier W, Hurlemann R. Oxytocin facilitates Pavlovian fear learning in males. *Neuropsychopharmacology* 41: 932–939, 2016. doi:10.1038/npp.2015.245.

302. Edmondson DG, Lyons GE, Martin JF, Olson EN. Mef2 gene expression marks the cardiac and skeletal muscle lineages during mouse embryogenesis. *Development* 120: 1251–1263, 1994.

303. Elabd C, Basillais A, Beaupied H, Breuil V, Wagner N, Scheideler M, Zaragosi LE, Massiéra F, Lemichez E, Trajanoski Z, Carle G, Euller-Ziegler L, Ailhaud G, Benhamou CL, Dani C, Amri EZ. Oxytocin controls differentiation of human mesenchymal stem cells and reverses osteoporosis. *Stem Cells* 26: 2399–2407, 2008. doi:10.1634/stemcells.2008-0127.

304. Elands J, Barberis C, Jard S, Tribollet E, Dreifuss JJ, Bankowski K, Manning M, Sawyer WH. 125I-labelled d(CH2)5[Tyr(Me)2,Thr4,Tyr-NH2(9)]OVT: a selective oxytocin receptor ligand. *Eur J Pharmacol* 147: 197–207, 1988. doi:10.1016/0014-2999(88)90778-9.

305. Eliava M, Melchior M, Knobloch-Bollmann HS, Wahis J, da Silva Gouveia M, Tang Y, Ciobanu AC, Triana Del Rio R, Roth LC, Althammer F, Chavant V, Goumon Y, Gruber T, Petit-Demoulière N, Busnelli M, Chini B, Tan LL, Mitre M, Froemke RC, Chao MV, Giese G, Sprengel R, Kuner R, Poisbeau P, Seeburg PH, Stoop R, Charlet A, Grinevich V. A new population of parvocellular oxytocin neurons controlling magnocellular neuron activity and inflammatory pain processing. *Neuron* 89: 1291–1304, 2016. doi:10.1016/j.neuron.2016.01.041.

306. Ely F, Petersen WE. Factors involved in the ejection of milk. *J Dairy Sci* 24: 211–223, 1941. doi:10.3168/jds.S0022-0302(41)95406-1.

307. Emanuele NV, Jurgens JK, Halloran MM, Tentler JJ, Lawrence AM, Kelley MR. The rat prolactin gene is expressed in brain tissue: detection of normal and alternatively spliced prolactin messenger RNA. *Mol Endocrinol* 6: 35–42, 1992.

308. Empson RM, Galione A. Cyclic ADP-ribose enhances coupling between voltage-gated Ca2+ entry and intracellular Ca2+ release. *J Biol Chem* 272: 20967–20970, 1997. doi:10.1074/jbc.272.34.20967.

309. Engelmann M, Ebner K, Landgraf R, Holsboer F, Wotjak CT I. Emotional stress triggers intrahypothalamic but not peripheral release of oxytocin in male rats. *J Neuroendocrinol* 11: 867–872, 1999. doi:10.1046/j.1365-2826.1999.00403.x.

310. Engelmann M, Ebner K, Landgraf R, Wotjak CT. Effects of Morris water maze testing on the neuroendocrine stress response and intrahypothalamic release of vasopressin and oxytocin in the rat. *Horm Behav* 50: 496–501, 2006. doi:10.1016/j.yhbeh.2006.04.009.

311. Engelmann M, Ebner K, Wotjak CT, Landgraf R. Endogenous oxytocin is involved in short-term olfactory memory in female rats. *Behav Brain Res* 90: 89–94, 1998. doi:10.1016/S0166-4328(97)00084-3.

312. Engelmann M, Landgraf R, Wotjak CT. The hypothalamic-neurohypophysial system regulates the hypothalamic-pituitary-adrenal axis under stress: an old concept revisited. *Front Neuroendocrinol* 25: 132–149, 2004. doi:10.1016/j.yfrne.2004.09.001.

313. Engelmann M, Wotjak CT, Landgraf R. Social discrimination procedure: an alternative method to investigate juvenile recognition abilities in rats. *Physiol Behav* 58: 315–321, 1995. doi:10.1016/0031-9384(95)00053-L.

314. Engelmann M, Wotjak CT, Neumann I, Ludwig M, Landgraf R. Behavioral consequences of intracerebral vasopressin and oxytocin: focus on learning and memory. *Neurosci Biobehav Rev* 20: 341–358, 1996. doi:10.1016/0149-7634(95)00059-3.

315. Ermisch A, Rühle HJ, Landgraf R, Hess J. Blood-brain barrier and peptides. *J Cereb Blood Flow Metab* 5: 350–357, 1985. doi:10.1038/jcbfm.1985.49.

316. Fahrbach SE, Morrell JI, Pfaff DW. Possible role for endogenous oxytocin in estrogen-facilitated maternal behavior in rats. *Neuroendocrinology* 40: 526–532, 1985. doi:10.1159/000124125.

317. Farooqi IS, O'Rahilly S. Monogenic obesity in humans. *Annu Rev Med* 56: 443–458, 2005. doi:10.1146/annurev.med.56.062904.144924.

318. Fehm-Wolfsdorf G, Bachholz G, Born J, Voigt K, Fehm HL. Vasopressin but not oxytocin enhances cortical arousal: an integrative hypothesis on behavioral effects of neurohypophyseal hormones. *Psychopharmacology (Berl)* 94: 496–500, 1988. doi:10.1007/BF00212844.

319. Feifel D, Macdonald K, Cobb P, Minassian A. Adjunctive intranasal oxytocin improves verbal memory in people with schizophrenia. *Schizophr Res* 139: 207–210, 2012. doi:10.1016/j.schres.2012.05.018.

320. Feifel D, Macdonald K, Nguyen A, Cobb P, Warlan H, Galangue B, Minassian A, Becker O, Cooper J, Perry W, Lefebvre M, Gonzales J, Hadley A. Adjunctive intranasal oxytocin reduces symptoms in schizophrenia patients. *Biol Psychiatry* 68: 678–680, 2010. doi:10.1016/j.biopsych.2010.04.039.

321. Feldman R, Gordon I, Zagoory-Sharon O. Maternal and paternal plasma, salivary, and urinary oxytocin and parent-infant synchrony: considering stress and affiliation components of human bonding. *Dev Sci* 14: 752–761, 2011. doi:10.1111/j.1467-7687.2010.01021.x.

322. Feldman R, Monakhov M, Pratt M, Ebstein RP. Oxytocin pathway genes: evolutionary ancient system impacting on human affiliation, sociality, and psychopathology. *Biol Psychiatry* 79: 174–184, 2016. doi:10.1016/j.biopsych.2015.08.008.

323. Feldman R, Weller A, Zagoory-Sharon O, Levine A. Evidence for a neuroendocrinological foundation of human affiliation: plasma oxytocin levels across pregnancy and the postpartum period predict mother-infant bonding. *Psychol Sci* 18: 965–970, 2007. doi:10.1111/j.1467-9280.2007.02010.x.

324. Feldman R, Zagoory-Sharon O, Weisman O, Schneiderman I, Gordon I, Maoz R, Shalev I, Ebstein RP. Sensitive parenting is associated with plasma oxytocin and polymorphisms in the OXTR and CD38 genes. *Biol Psychiatry* 72: 175–181, 2012. doi:10.1016/j.biopsych.2011.12.025.

325. Ferguson AV, Latchford KJ, Samson WK. The paraventricular nucleus of the hypothalamus - a potential target for integrative treatment of autonomic dysfunction. *Expert Opin Ther Targets* 12: 717–727, 2008. doi:10.1517/14728222.12.6.717.

326. Ferguson J. A study of the motility of the intact uterus at term. *Surg Gynecol Obstet* 73: 73, 1941.

327. Ferguson JN, Aldag JM, Insel TR, Young LJ. Oxytocin in the medial amygdala is essential for social recognition in the mouse. *J Neurosci* 21: 8278–8285, 2001.

328. Ferguson JN, Young LJ, Hearn EF, Matzuk MM, Insel TR, Winslow JT. Social amnesia in mice lacking the oxytocin gene. *Nat Genet* 25: 284–288, 2000. doi:10.1038/77040.

329. Fernández-Guasti A, Roldán-Roldán G, Saldívar A. Reduction in anxiety after ejaculation in the rat. *Behav Brain Res* 32: 23–29, 1989. doi:10.1016/S0166-4328(89)80068-3.

330. Fernando RN, Larm J, Albiston AL, Chai SY. Distribution and cellular localization of insulin-regulated aminopeptidase in the rat central nervous system. *J Comp Neurol* 487: 372–390, 2005. doi:10.1002/cne.20585.

331. Ferrier BM, Kennett DJ, Devlin MC. Influence of oxytocin on human memory processes. *Life Sci* 27: 2311–2317, 1980. doi:10.1016/0024-3205(80)90499-3.

332. Ferris CF, Foote KB, Meltser HM, Plenby MG, Smith KL, Insel TR. Oxytocin in the amygdala facilitates maternal aggression. *Ann N Y Acad Sci* 652: 456–457, 1992. doi:10.1111/j.1749-6632.1992.tb34382.x.

333. Fetissov SO, Hallman J, Nilsson I, Lefvert AK, Oreland L, Hökfelt T. Aggressive behavior linked to corticotropin-reactive autoantibodies. *Biol Psychiatry* 60: 799–802, 2006. doi:10.1016/j.biopsych.2006.03.081.

334. Fields RL, Gainer H. The −216- to −100-bp sequence in the 5′-flanking region of the oxytocin gene contains a cell-type specific regulatory element for its selective expression in oxytocin magnocellular neurones. *J Neuroendocrinol* 27: 702–707, 2015. doi:10.1111/jne.12299.

335. Fields RL, Ponzio TA, Kawasaki M, Gainer H. Cell-type specific oxytocin gene expression from AAV delivered promoter deletion constructs into the rat supraoptic nucleus in vivo. *PLoS One* 7: e32085, 2012. doi:10.1371/journal.pone.0032085.

336. Finsterwald C, Fiumelli H, Cardinaux JR, Martin JL. Regulation of dendritic development by BDNF requires activation of CRTC1 by glutamate. *J Biol Chem* 285: 28587–28595, 2010. doi:10.1074/jbc.M110.125740.

337. Fischmann TO, Smith CK, Mayhood TW, Myers JE, Reichert P, Mannarino A, Carr D, Zhu H, Wong J, Yang RS, Le HV, Madison VS. Crystal structures of MEK1 binary and ternary complexes with nucleotides and inhibitors. *Biochemistry* 48: 2661–2674, 2009. doi:10.1021/bi801898e.

338. Fisher TE, Bourque CW. Calcium-channel subtypes in the somata and axon terminals of magnocellular neurosecretory cells. *Trends Neurosci* 19: 440–444, 1996. doi:10.1016/0166-2236(96)10034-5.

339. Flanagan-Cato LM. Sex differences in the neural circuit that mediates female sexual receptivity. *Front Neuroendocrinol* 32: 124–136, 2011. doi:10.1016/j.yfrne.2011.02.008.

340. Flanagan LM, Dohanics J, Verbalis JG, Stricker EM. Gastric motility and food intake in rats after lesions of hypothalamic paraventricular nucleus. *Am J Physiol Regul Integr Comp Physiol* 263: R39–R44, 1992.

341. Flanagan LM, Olson BR, Sved AF, Verbalis JG, Stricker EM. Gastric motility in conscious rats given oxytocin and an oxytocin antagonist centrally. *Brain Res* 578: 256–260, 1992. doi:10.1016/0006-8993(92)90255-8.

342. Flanagan LM, Pfaus JG, Pfaff DW, McEwen BS. Induction of FOS immunoreactivity in oxytocin neurons after sexual activity in female rats. *Neuroendocrinology* 58: 352–358, 1993. doi:10.1159/000126562.

343. Flavell SW, Cowan CW, Kim TK, Greer PL, Lin Y, Paradis S, Griffith EC, Hu LS, Chen C, Greenberg ME. Activity-dependent regulation of MEF2 transcription factors suppresses excitatory synapse number. *Science* 311: 1008–1012, 2006. doi:10.1126/science.1122511.

344. Flavell SW, Greenberg ME. Signaling mechanisms linking neuronal activity to gene expression and plasticity of the nervous system. *Annu Rev Neurosci* 31: 563–590, 2008. doi:10.1146/annurev.neuro.31.060407.125631.

345. Flavell SW, Kim TK, Gray JM, Harmin DA, Hemberg M, Hong EJ, Markenscoff-Papadimitriou E, Bear DM, Greenberg ME. Genome-wide analysis of MEF2 transcriptional program reveals synaptic target genes and neuronal activity-dependent polyadenylation site selection. *Neuron* 60: 1022–1038, 2008. doi:10.1016/j.neuron.2008.11.029.

346. Fleming Y, Armstrong CG, Morrice N, Paterson A, Goedert M, Cohen P. Synergistic activation of stress-activated protein kinase 1/c-Jun N-terminal kinase (SAPK1/JNK) isoforms by mitogen-activated protein kinase kinase 4 (MKK4) and MKK7. *Biochem J* 352: 145–154, 2000. doi:10.1042/bj3520145.

347. Florian M, Jankowski M, Gutkowska J. Oxytocin increases glucose uptake in neonatal rat cardiomyocytes. *Endocrinology* 151: 482–491, 2010. doi:10.1210/en.2009-0624.

348. Foehring RC, Armstrong WE. Pharmacological dissection of high-voltage-activated Ca2+ current types in acutely dissociated rat supraoptic magnocellular neurons. *J Neurophysiol* 76: 977–983, 1996. doi:10.1152/jn.1996.76.2.977.

349. Forsling ML, Taverne MA, Parvizi N, Elsaesser F, Smidt D, Ellendorff F. Plasma oxytocin and steroid concentrations during late pregnancy, parturition and lactation in the miniature pig. *J Endocrinol* 82: 61–69, 1979. doi:10.1677/joe.0.0820061.

350. Francis DD, Young LJ, Meaney MJ, Insel TR. Naturally occurring differences in maternal care are associated with the expression of oxytocin and vasopressin (V1a) receptors: gender differences. *J Neuroendocrinol* 14: 349–353, 2002. doi:10.1046/j.0007-1331.2002.00776.x.

351. Frank E, Landgraf R. The vasopressin system—from antidiuresis to psychopathology. *Eur J Pharmacol* 583: 226–242, 2008. doi:10.1016/j.ejphar.2007.11.063.

352. Frasch A, Zetzsche T, Steiger A, Jirikowski GF. Reduction of plasma oxytocin levels in patients suffering from major depression. *Adv Exp Med Biol* 395: 257–258, 1995.

353. Frazer KA, Ballinger DG, Cox DR, Hinds DA, Stuve LL, Gibbs RA, Belmont JW, Boudreau A, Hardenbol P, Leal SM, Pasternak S, Wheeler DA, Willis TD, Yu F, Yang H, Zeng C, Gao Y, Hu H, Hu W, Li C, Lin W, Liu S, Pan H, Tang X, Wang J, Wang W, Yu J, Zhang B, Zhang Q, Zhao H, Zhao H, Zhou J, Gabriel SB, Barry R, Blumenstiel B, Camargo A, Defelice M, Faggart M, Goyette M, Gupta S, Moore J, Nguyen H, Onofrio RC, Parkin M, Roy J, Stahl E, Winchester E, Ziaugra L, Altshuler D, Shen Y, Yao Z, Huang W, Chu X, He Y, Jin L, Liu Y, Shen Y, Sun W, Wang H, Wang Y, Wang Y, Xiong X, Xu L, Waye MM, Tsui SK, Xue H, Wong JT, Galver LM, Fan JB, Gunderson K, Murray SS, Oliphant AR, Chee MS, Montpetit A, Chagnon F, Ferretti V, Leboeuf M, Olivier JF, Phillips MS, Roumy S, Sallée C, Verner A, Hudson TJ, Kwok PY, Cai D, Koboldt DC, Miller RD, Pawlikowska L, Taillon-Miller P, Xiao M, Tsui LC, Mak W, Song YQ, Tam PK, Nakamura Y, Kawaguchi T, Kitamoto T, Morizono T, Nagashima A, Ohnishi Y, Sekine A, Tanaka T, Tsunoda T, Deloukas P, Bird CP, Delgado M, Dermitzakis ET, Gwilliam R, Hunt S, Morrison J, Powell D, Stranger BE, Whittaker P, Bentley DR, Daly MJ, de Bakker PI, Barrett J, Chretien YR, Maller J, McCarroll S, Patterson N, Pe'er I, Price A, Purcell S, Richter DJ, Sabeti P, Saxena R, Schaffner SF, Sham PC, Varilly P, Altshuler D, Stein LD, Krishnan L, Smith AV, Tello-Ruiz MK, Thorisson GA, Chakravarti A, Chen PE, Cutler DJ, Kashuk CS, Lin S, Abecasis GR, Guan W, Li Y, Munro HM, Qin ZS, Thomas DJ, McVean G, Auton A, Bottolo L, Cardin N, Eyheramendy S, Freeman C, Marchini J, Myers S, Spencer C, Stephens M, Donnelly P, Cardon LR, Clarke G, Evans DM, Morris AP, Weir BS, Tsunoda T, Mullikin JC, Sherry ST, Feolo M, Skol A, Zhang H, Zeng C, Zhao H, Matsuda I, Fukushima Y, Macer DR, Suda E, Rotimi CN, Adebamowo CA, Ajayi I, Aniagwu T, Marshall PA, Nkwodimmah C, Royal CD, Leppert MF, Dixon M, Peiffer A, Qiu R, Kent A, Kato K, Niikawa N, Adewole IF, Knoppers BM, Foster MW, Clayton EW, Watkin J, Gibbs RA, Belmont JW, Muzny D, Nazareth L, Sodergren E, Weinstock GM, Wheeler DA, Yakub I, Gabriel SB, Onofrio RC, Richter DJ, Ziaugra L, Birren BW, Daly MJ, Altshuler D, Wilson RK, Fulton LL, Rogers J, Burton J, Carter NP, Clee CM, Griffiths M, Jones MC, McLay K, Plumb RW, Ross MT, Sims SK, Willey DL, Chen Z, Han H, Kang L, Godbout M, Wallenburg JC, L'Archevêque P, Bellemare G, Saeki K, Wang H, An D, Fu H, Li Q, Wang Z, Wang R, Holden AL, Brooks LD, McEwen JE, Guyer MS, Wang VO, Peterson JL, Shi M, Spiegel J, Sung LM, Zacharia LF, Collins FS, Kennedy K, Jamieson R, Stewart J; International HapMap Consortium. A second generation human haplotype map of over 3.1 million SNPs. *Nature* 449: 851–861, 2007. doi:10.1038/nature06258.

354. Freeman SM, Inoue K, Smith AL, Goodman MM, Young LJ. The neuroanatomical distribution of oxytocin receptor binding and mRNA in the male rhesus macaque (Macaca mulatta). *Psychoneuroendocrinology* 45: 128–141, 2014. doi:10.1016/j.psyneuen.2014.03.023.

355. Freeman SM, Walum H, Inoue K, Smith AL, Goodman MM, Bales KL, Young LJ. Neuroanatomical distribution of oxytocin and vasopressin 1a receptors in the socially monogamous coppery titi monkey (Callicebus cupreus). *Neuroscience* 273: 12–23, 2014. doi:10.1016/j.neuroscience.2014.04.055.

356. French JA, Taylor JH, Mustoe AC, Cavanaugh J. Neuropeptide diversity and the regulation of social behavior in New World primates. *Front Neuroendocrinol* 42: 18–39, 2016. doi:10.1016/j.yfrne.2016.03.004.

357. Freund-Mercier MJ, Stoeckel ME, Klein MJ. Oxytocin receptors on oxytocin neurones: histoautoradiographic detection in the lactating rat. *J Physiol* 480: 155–161, 1994. doi:10.1113/jphysiol.1994.sp020349.

358. Freund-Mercier MJ, Stoeckel ME, Palacios JM, Pazos A, Reichhart JM, Porte A, Richard P. Pharmacological characteristics and anatomical distribution of [3H]oxytocin-binding sites in the Wistar rat brain studied by autoradiography. *Neuroscience* 20: 599–614, 1987. doi:10.1016/0306-4522(87)90113-8.

359. Wismer Fries AB, Ziegler TE, Kurian JR, Jacoris S, Pollak SD. Early experience in humans is associated with changes in neuropeptides critical for regulating social behavior. *Proc Natl Acad Sci USA* 102: 17237–17240, 2005. doi:10.1073/pnas.0504767102.

360. Fuchs AR, Dawood MY. Oxytocin release and uterine activation during parturition iin rabbits. *Endocrinology* 107: 1117–1126, 1980. doi:10.1210/endo-107-4-1117.

361. Fuchs AR, Fields MJ, Freidman S, Shemesh M, Ivell R. Oxytocin and the timing of parturition. Influence of oxytocin receptor gene expression, oxytocin secretion, and oxytocin-induced prostaglandin F2 alpha and E2 release. *Adv Exp Med Biol* 395: 405–420, 1995.

362. Gaetani S, Fu J, Cassano T, Dipasquale P, Romano A, Righetti L, Cianci S, Laconca L, Giannini E, Scaccianoce S, Mairesse J, Cuomo V, Piomelli D. The fat-induced satiety factor oleoylethanolamide suppresses feeding through central release of oxytocin. *J Neurosci* 30: 8096–8101, 2010. doi:10.1523/JNEUROSCI.0036-10.2010.

363. Gainer H, Sarne Y, Brownstein MJ. Neurophysin biosynthesis: conversion of a putative precursor during axonal transport. *Science* 195: 1354–1356, 1977. doi:10.1126/science.65791.

364. Gainer H, Yamashita M, Fields RL, House SB, Rusnak M. The magnocellular neuronal phenotype: cell-specific gene expression in the hypothalamo-neurohypophysial system. *Prog Brain Res* 139: 1–14, 2002. doi:10.1016/S0079-6123(02)39003-4.

365. Gálfi M, Radács M, Juhász A, László F, Molnár A, László FA. Serotonin-induced enhancement of vasopressin and oxytocin secretion in rat neurohypophyseal tissue culture. *Regul Pept* 127: 225–231, 2005. doi:10.1016/j.regpep.2004.12.009.

366. Gao FB. Messenger RNAs in dendrites: localization, stability, and implications for neuronal function. *BioEssays* 20: 70–78, 1998. doi:10.1002/(SICI)1521-1878(199801)20:1<70::AID-BIES10>3.0.CO;2-5.

367. Gard PR, Daw P, Mashhour ZS, Tran P. Interactions of angiotensin IV and oxytocin on behaviour in mice. *J Renin Angiotensin Aldosterone Syst* 8: 133–138, 2007. doi:10.3317/jraas.2007.016.

368. Gard PR, Naylor C, Ali S, Partington C. Blockade of pro-cognitive effects of angiotensin IV and physostigmine in mice by oxytocin antagonism. *Eur J Pharmacol* 683: 155–160, 2012. doi:10.1016/j.ejphar.2012.02.048.

369. Gazis D. Plasma half-lives of vasopressin and oxytocin analogs after iv injection in rats. *Proc Soc Exp Biol Med* 158: 663–665, 1978. doi:10.3181/00379727-158-40269.

370. Geisler S, Wise RA. Functional implications of glutamatergic projections to the ventral tegmental area. *Rev Neurosci* 19: 227–244, 2008. doi:10.1515/REVNEURO.2008.19.4-5.227.

371. Georgescu M, Pfaus JG. Role of glutamate receptors in the ventromedial hypothalamus in the regulation of female rat sexual behaviors I. Behavioral effects of glutamate and its selective receptor agonists AMPA, NMDA and kainate. *Pharmacol Biochem Behav* 83: 322–332, 2006. doi:10.1016/j.pbb.2006.02.016.

372. Gerendai I, Tóth IE, Kocsis K, Boldogkoi Z, Rusvai M, Halász B. Identification of CNS neurons involved in the innervation of the epididymis: a viral transneuronal tracing study. *Auton Neurosci* 92: 1–10, 2001. doi:10.1016/S1566-0702(01)00292-2.

373. Gibbs DM. Dissociation of oxytocin, vasopressin and corticotropin secretion during different types of stress. *Life Sci* 35: 487–491, 1984. doi:10.1016/0024-3205(84)90241-8.

374. Gil M, Bhatt R, Picotte KB, Hull EM. Oxytocin in the medial preoptic area facilitates male sexual behavior in the rat. *Horm Behav* 59: 435–443, 2011. doi:10.1016/j.yhbeh.2010.12.012.

375. Gil M, Bhatt R, Picotte KB, Hull EM. Sexual experience increases oxytocin receptor gene expression and protein in the medial preoptic area of the male rat. *Psychoneuroendocrinology* 38: 1688–1697, 2013. doi:10.1016/j.psyneuen.2013.02.002.

376. Gilbert CL, Goode JA, McGrath TJ. Pulsatile secretion of oxytocin during parturition in the pig: temporal relationship with fetal expulsion. *J Physiol* 475: 129–137, 1994. doi:10.1113/jphysiol.1994.sp020054.

377. Gilbert CL, Jenkins K, Wathes DC. Pulsatile release of oxytocin into the circulation of the ewe during oestrus, mating and the early luteal phase. *J Reprod Fertil* 91: 337–346, 1991. doi:10.1530/jrf.0.0910337.

378. Gimpl G, Fahrenholz F. The oxytocin receptor system: structure, function, and regulation. *Physiol Rev* 81: 629–683, 2001. doi:10.1152/physrev.2001.81.2.629.

379. Gimpl G, Postina R, Fahrenholz F, Reinheimer T. Binding domains of the oxytocin receptor for the selective oxytocin receptor antagonist barusiban in comparison to the agonists oxytocin and carbetocin. *Eur J Pharmacol* 510: 9–16, 2005. doi:10.1016/j.ejphar.2005.01.010.

380. Giraldi A, Rellini AH, Pfaus J, Laan E. Female sexual arousal disorders. *J Sex Med* 10: 58–73, 2013. doi:10.1111/j.1743-6109.2012.02820.x.

381. Giuliano F, Bernabé J, McKenna K, Longueville F, Rampin O. Spinal proerectile effect of oxytocin in anesthetized rats. *Am J Physiol Regul Integr Comp Physiol* 280: R1870–R1877, 2001. doi:10.1152/ajpregu.2001.280.6.R1870.

382. Gomez N, Erazo T, Lizcano JM. ERK5 and Cell Proliferation: Nuclear Localization Is What Matters. *Front Cell Dev Biol* 4: 105, 2016. doi:10.3389/fcell.2016.00105.

383. Gong X, Tang X, Wiedmann M, Wang X, Peng J, Zheng D, Blair LA, Marshall J, Mao Z. Cdk5-mediated inhibition of the protective effects of transcription factor MEF2 in neurotoxicity-induced apoptosis. *Neuron* 38: 33–46, 2003. doi:10.1016/S0896-6273(03)00191-0.

384. Goodman OB Jr, Krupnick JG, Santini F, Gurevich VV, Penn RB, Gagnon AW, Keen JH, Benovic JL. Beta-arrestin acts as a clathrin adaptor in endocytosis of the beta2-adrenergic receptor. *Nature* 383: 447–450, 1996. doi:10.1038/383447a0.

385. Goodson JL. Nonapeptides and the evolutionary patterning of sociality. *Prog Brain Res* 170: 3–15, 2008. doi:10.1016/S0079-6123(08)00401-9.

386. Gorbulev V, Büchner H, Akhundova A, Fahrenholz F. Molecular cloning and functional characterization of V2 [8-lysine] vasopressin and oxytocin receptors from a pig kidney cell line. *Eur J Biochem* 215: 1–7, 1993. doi:10.1111/j.1432-1033.1993.tb18000.x.

387. Gordon I, Zagoory-Sharon O, Leckman JF, Feldman R. Oxytocin and the development of parenting in humans. *Biol Psychiatry* 68: 377–382, 2010. doi:10.1016/j.biopsych.2010.02.005.

388. Gorka SM, Fitzgerald DA, Labuschagne I, Hosanagar A, Wood AG, Nathan PJ, Phan KL. Oxytocin modulation of amygdala functional connectivity to fearful faces in generalized social anxiety disorder. *Neuropsychopharmacology* 40: 278–286, 2015. doi:10.1038/npp.2014.168.

389. Gould BR, Zingg HH. Mapping oxytocin receptor gene expression in the mouse brain and mammary gland using an oxytocin receptor-LacZ reporter mouse. *Neuroscience* 122: 155–167, 2003. doi:10.1016/S0306-4522(03)00283-5.

390. Gouraud SS, Yao ST, Heesom KJ, Paton JF, Murphy D. 14–3-3 proteins within the hypothalamic-neurohypophyseal system of the osmotically stressed rat: transcriptomic and proteomic studies. *J Neuroendocrinol* 19: 913–922, 2007. doi:10.1111/j.1365-2826.2007.01604.x.

391. Gouzènes L, Desarménien MG, Hussy N, Richard P, Moos FC. Vasopressin regularizes the phasic firing pattern of rat hypothalamic magnocellular vasopressin neurons. *J Neurosci* 18: 1879–1885, 1998.

392. Gravati M, Busnelli M, Bulgheroni E, Reversi A, Spaiardi P, Parenti M, Toselli M, Chini B. Dual modulation of inward rectifier potassium currents in olfactory neuronal cells by promiscuous G protein coupling of the oxytocin receptor. *J Neurochem* 114: 1424–1435, 2010.

393. Greenwood MA, Hammock EA. Oxytocin receptor binding sites in the periphery of the neonatal mouse. *PLoS One* 12: e0172904, 2017. doi:10.1371/journal.pone.0172904.

394. Griffin GD, Ferri-Kolwicz SL, Reyes BA, Van Bockstaele EJ, Flanagan-Cato LM. Ovarian hormone-induced reorganization of oxytocin-labeled dendrites and synapses lateral to the hypothalamic ventromedial nucleus in female rats. *J Comp Neurol* 518: 4531–4545, 2010. doi:10.1002/cne.22470.

395. Griffin MG, Taylor GT. Norepinephrine modulation of social memory: evidence for a time-dependent functional recovery of behavior. *Behav Neurosci* 109: 466–473, 1995. doi:10.1037/0735-7044.109.3.466.

396. Grillon C, Krimsky M, Charney DR, Vytal K, Ernst M, Cornwell B. Oxytocin increases anxiety to unpredictable threat. *Mol Psychiatry* 18: 958–960, 2013. doi:10.1038/mp.2012.156.

397. Grinevich V, Desarménien MG, Chini B, Tauber M, Muscatelli F. Ontogenesis of oxytocin pathways in the mammalian brain: late maturation and psychosocial disorders. *Front Neuroanat* 8: 164, 2015. doi:10.3389/fnana.2014.00164.

398. Grinevich V, Knobloch-Bollmann HS, Eliava M, Busnelli M, Chini B. Assembling the puzzle: pathways of oxytocin signaling in the brain. *Biol Psychiatry* 79: 155–164, 2016. doi:10.1016/j.biopsych.2015.04.013.

399. Grippo AJ, Trahanas DM, Zimmerman RR II, Porges SW, Carter CS. Oxytocin protects against negative behavioral and autonomic consequences of long-term social isolation. *Psychoneuroendocrinology* 34: 1542–1553, 2009. doi:10.1016/j.psyneuen.2009.05.017.

400. Gronroos M, Kivikoski A, Kyostila J. [On the effect of intranasally administered oxytocin (syntocin) on lactation]. *Ann Chir Gynaecol Fenn* 51: 377–381, 1962.

401. Grotegut CA, Feng L, Mao L, Heine RP, Murtha AP, Rockman HA. β-Arrestin mediates oxytocin receptor signaling, which regulates uterine contractility and cellular migration. *Am J Physiol Endocrinol Metab* 300: E468–E477, 2011. doi:10.1152/ajpendo.00390.2010.

402. Grotegut CA, Mao L, Pierce SL, Swamy GK, Heine RP, Murtha AP. Enhanced uterine contractility and stillbirth in mice lacking G protein-coupled receptor kinase 6 (GRK6): implications for oxytocin receptor desensitization. *Mol Endocrinol* 30: 455–468, 2016. doi:10.1210/me.2015-1147.

403. Guastella AJ, Carson DS, Dadds MR, Mitchell PB, Cox RE. Does oxytocin influence the early detection of angry and happy faces? *Psychoneuroendocrinology* 34: 220–225, 2009. doi:10.1016/j.psyneuen.2008.09.001.

404. Guastella AJ, Howard AL, Dadds MR, Mitchell P, Carson DS. A randomized controlled trial of intranasal oxytocin as an adjunct to exposure therapy for social anxiety disorder. *Psychoneuroendocrinology* 34: 917–923, 2009. doi:10.1016/j.psyneuen.2009.01.005.

405. Guastella AJ, MacLeod C. A critical review of the influence of oxytocin nasal spray on social cognition in humans: evidence and future directions. *Horm Behav* 61: 410–418, 2012. doi:10.1016/j.yhbeh.2012.01.002.

406. Günther R, Landgraf R, Köppe I. [Cystine aminopeptidase and oxytocin in the plasma of pregnant patients with premature labor]. *Zentralbl Gynakol* 107: 1178–1185, 1985.

407. Gur R, Tendler A, Wagner S. Long-term social recognition memory is mediated by oxytocin-dependent synaptic plasticity in the medial amygdala. *Biol Psychiatry* 76: 377–386, 2014. doi:10.1016/j.biopsych.2014.03.022.

408. Gutkowska J, Jankowski M. Oxytocin revisited: its role in cardiovascular regulation. *J Neuroendocrinol* 24: 599–608, 2012. doi:10.1111/j.1365-2826.2011.02235.x.

409. Gutkowska J, Jankowski M, Antunes-Rodrigues J. The role of oxytocin in cardiovascular regulation. *Rev Bras Pesqui Med Biol* 47: 206–214, 2014.

410. Guzmán YF, Tronson NC, Jovasevic V, Sato K, Guedea AL, Mizukami H, Nishimori K, Radulovic J. Fear-enhancing effects of septal oxytocin receptors. *Nat Neurosci* 16: 1185–1187, 2013. doi:10.1038/nn.3465.

411. Halbach P, Pillers DA, York N, Asuma MP, Chiu MA, Luo W, Tokarz S, Bird IM, Pattnaik BR. Oxytocin expression and function in the posterior retina: a novel signaling pathway. *Invest Ophthalmol Vis Sci* 56: 751–760, 2015. doi:10.1167/iovs.14-15646.

412. Hall SS, Lightbody AA, McCarthy BE, Parker KJ, Reiss AL. Effects of intranasal oxytocin on social anxiety in males with fragile X syndrome. *Psychoneuroendocrinology* 37: 509–518, 2012. doi:10.1016/j.psyneuen.2011.07.020.

413. Haller J, Harold G, Sandi C, Neumann ID. Effects of adverse early-life events on aggression and anti-social behaviours in animals and humans. *J Neuroendocrinol* 26: 724–738, 2014. doi:10.1111/jne.12182.

414. Hamamura M, Leng G, Emson PC, Kiyama H. Electrical activation and c-fos mRNA expression in rat neurosecretory neurones after systemic administration of cholecystokinin. *J Physiol* 444: 51–63, 1991. doi:10.1113/jphysiol.1991.sp018865.

415. Han J, Jiang Y, Li Z, Kravchenko VV, Ulevitch RJ. Activation of the transcription factor MEF2C by the MAP kinase p38 in inflammation. *Nature* 386: 296–299, 1997. doi:10.1038/386296a0.

416. Han WY, Du P, Fu SY, Wang F, Song M, Wu CF, Yang JY. Oxytocin via its receptor affects restraint stress-induced methamphetamine CPP reinstatement in mice: Involvement of the medial prefrontal cortex and dorsal hippocampus glutamatergic system. *Pharmacol Biochem Behav* 119: 80–87, 2014. doi:10.1016/j.pbb.2013.11.014.

417. Haque M, Wilson R, Sharma K, Mills NJ, Teruyama R. Localisation of 11β-hydroxysteroid dehydrogenase type 2 in mineralocorticoid receptor expressing magnocellular neurosecretory neurones of the rat supraoptic and paraventricular nuclei. *J Neuroendocrinol* 27: 835–849, 2015. doi:10.1111/jne.12325.

418. Haram M, Tesli M, Bettella F, Djurovic S, Andreassen OA, Melle I. Association between genetic variation in the oxytocin receptor gene and emotional withdrawal, but not between oxytocin pathway genes and diagnosis in psychotic disorders. *Front Hum Neurosci* 9: 9, 2015. doi:10.3389/fnhum.2015.00009.

419. Hard E, Hansen S. Reduced fearfulness in the lactating rat. *Physiol Behav* 35: 641–643, 1985. doi:10.1016/0031-9384(85)90155-6.

420. Harden SW, Frazier CJ. Oxytocin depolarizes fast-spiking hilar interneurons and induces GABA release onto mossy cells of the rat dentate gyrus. *Hippocampus* 26: 1124–1139, 2016. doi:10.1002/hipo.22595.

421. Harmer CJ, Bhagwagar Z, Perrett DI, Völlm BA, Cowen PJ, Goodwin GM. Acute SSRI administration affects the processing of social cues in healthy volunteers. *Neuropsychopharmacology* 28: 148–152, 2003. doi:10.1038/sj.npp.1300004.

422. Harmer CJ, Mackay CE, Reid CB, Cowen PJ, Goodwin GM. Antidepressant drug treatment modifies the neural processing of nonconscious threat cues. *Biol Psychiatry* 59: 816–820, 2006. doi:10.1016/j.biopsych.2005.10.015.

423. Harmon AC, Huhman KL, Moore TO, Albers HE. Oxytocin inhibits aggression in female Syrian hamsters. *J Neuroendocrinol* 14: 963–969, 2002. doi:10.1046/j.1365-2826.2002.00863.x.

424. Harony-Nicolas H, Mamrut S, Brodsky L, Shahar-Gold H, Barki-Harrington L, Wagner S. Brain region-specific methylation in the promoter of the murine oxytocin receptor gene is involved in its expression regulation. *Psychoneuroendocrinology* 39: 121–131, 2014. doi:10.1016/j.psyneuen.2013.10.004.

425. Hasbi A, Devost D, Laporte SA, Zingg HH. Real-time detection of interactions between the human oxytocin receptor and G protein-coupled receptor kinase-2. *Mol Endocrinol* 18: 1277–1286, 2004. doi:10.1210/me.2003-0440.

426. Hathaway GA, Faykoo-Martinez M, Peragine DE, Mooney SJ, Holmes MM. Subcaste differences in neural activation suggest a prosocial role for oxytocin in eusocial naked mole-rats. *Horm Behav* 79: 1–7, 2016. doi:10.1016/j.yhbeh.2015.12.001.

427. Hatton GI. Emerging concepts of structure-function dynamics in adult brain: the hypothalamo-neurohypophysial system. *Prog Neurobiol* 34: 437–504, 1990. doi:10.1016/0301-0082(90)90017-B.

428. Hatton GI, Wang YF. Neural mechanisms underlying the milk ejection burst and reflex. *Prog Brain Res* 170: 155–166, 2008. doi:10.1016/S0079-6123(08)00414-7.

429. Hattori T, Kanno K, Nagasawa M, Nishimori K, Mogi K, Kikusui T. Impairment of interstrain social recognition during territorial aggressive behavior in oxytocin receptor-null mice. *Neurosci Res* 90: 90–94, 2015. doi:10.1016/j.neures.2014.05.003.

430. Hattori T, Sundberg DK, Morris M. Central and systemic oxytocin release: a study of the paraventricular nucleus by in vivo microdialysis. *Brain Res Bull* 28: 257–263, 1992. doi:10.1016/0361-9230(92)90187-3.

431. Havranek T, Zatkova M, Lestanova Z, Bacova Z, Mravec B, Hodosy J, Strbak V, Bakos J. Intracerebroventricular oxytocin administration in rats enhances object recognition and increases expression of neurotrophins, microtubule-associated protein 2, and synapsin I. *J Neurosci Res* 93: 893–901, 2015. doi:10.1002/jnr.23559.

432. Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. *Biol Psychiatry* 54: 1389–1398, 2003. doi:10.1016/S0006-3223(03)00465-7.

433. Heinrichs M, Meinlschmidt G, Neumann I, Wagner S, Kirschbaum C, Ehlert U, Hellhammer DH. Effects of suckling on hypothalamic-pituitary-adrenal axis responses to psychosocial stress in postpartum lactating women. *J Clin Endocrinol Metab* 86: 4798–4804, 2001. doi:10.1210/jcem.86.10.7919.

434. Heinrichs M, Meinlschmidt G, Wippich W, Ehlert U, Hellhammer DH. Selective amnesic effects of oxytocin on human memory. *Physiol Behav* 83: 31–38, 2004. doi:10.1016/S0031-9384(04)00346-4.

435. Heinrichs M, Neumann I, Ehlert U. Lactation and stress: protective effects of breast-feeding in humans. *Stress* 5: 195–203, 2002. doi:10.1080/1025389021000010530.

436. Herman JP, Figueiredo H, Mueller NK, Ulrich-Lai Y, Ostrander MM, Choi DC, Cullinan WE. Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. *Front Neuroendocrinol* 24: 151–180, 2003. doi:10.1016/j.yfrne.2003.07.001.

437. Herzmann G, Bird CW, Freeman M, Curran T. Effects of oxytocin on behavioral and ERP measures of recognition memory for own-race and other-race faces in women and men. *Psychoneuroendocrinology* 38: 2140–2151, 2013. doi:10.1016/j.psyneuen.2013.04.002.

438. Herzmann G, Young B, Bird CW, Curran T. Oxytocin can impair memory for social and non-social visual objects: a within-subject investigation of oxytocin's effects on human memory. *Brain Res* 1451: 65–73, 2012. doi:10.1016/j.brainres.2012.02.049.

439. Hew-Butler T, Noakes TD, Soldin SJ, Verbalis JG. Acute changes in endocrine and fluid balance markers during high-intensity, steady-state, and prolonged endurance running: unexpected increases in oxytocin and brain natriuretic peptide during exercise. *Eur J Endocrinol* 159: 729–737, 2008. doi:10.1530/EJE-08-0064.

440. Hicks C, Jorgensen W, Brown C, Fardell J, Koehbach J, Gruber CW, Kassiou M, Hunt GE, McGregor IS. The nonpeptide oxytocin receptor agonist WAY 267,464: receptor-binding profile, prosocial effects and distribution of c-Fos expression in adolescent rats. *J Neuroendocrinol* 24: 1012–1029, 2012. doi:10.1111/j.1365-2826.2012.02311.x.

441. Hidema S, Fukuda T, Hiraoka Y, Mizukami H, Hayashi R, Otsuka A, Suzuki S, Miyazaki S, Nishimori K. Generation of Oxtr cDNA(HA)-Ires-Cre mice for gene expression in an oxytocin receptor specific manner. *J Cell Biochem* 117: 1099–1111, 2016. doi:10.1002/jcb.25393.

442. Higashida H. Somato-axodendritic release of oxytocin into the brain due to calcium amplification is essential for social memory. *J Physiol Sci* 66: 275–282, 2015. doi:10.1007/s12576-015-0425-0.

443. Higashida H, Robbins J, Egorova A, Noda M, Taketo M, Ishizaka N, Takasawa S, Okamoto H, Brown DA. Nicotinamide-adenine dinucleotide regulates muscarinic receptor-coupled K+ (M) channels in rodent NG108–15 cells. *J Physiol* 482: 317–323, 1995. doi:10.1113/jphysiol.1995.sp020520.

444. Higashida H, Yokoyama S, Huang JJ, Liu L, Ma WJ, Akther S, Higashida C, Kikuchi M, Minabe Y, Munesue T. Social memory, amnesia, and autism: brain oxytocin secretion is regulated by NAD+ metabolites and single nucleotide polymorphisms of CD38. *Neurochem Int* 61: 828–838, 2012. doi:10.1016/j.neuint.2012.01.030.

445. Higashida H, Yokoyama S, Kikuchi M, Munesue T. CD38 and its role in oxytocin secretion and social behavior. *Horm Behav* 61: 351–358, 2012. doi:10.1016/j.yhbeh.2011.12.011.

446. Higuchi T, Honda K, Fukuoka T, Negoro H, Hosono Y, Nishida E. Pulsatile secretion of prolactin and oxytocin during nursing in the lactating rat. *Endocrinol Jpn* 30: 353–359, 1983. doi:10.1507/endocrj1954.30.353.

447. Hillegaart V, Alster P, Uvnäs-Moberg K, Ahlenius S. Sexual motivation promotes oxytocin secretion in male rats. *Peptides* 19: 39–45, 1998. doi:10.1016/S0196-9781(97)00250-7.

448. Hoffman ER, Brownley KA, Hamer RM, Bulik CM. Plasma, salivary, and urinary oxytocin in anorexia nervosa: a pilot study. *Eat Behav* 13: 256–259, 2012. doi:10.1016/j.eatbeh.2012.02.004.

449. Hökfelt T, Herrera-Marschitz M, Seroogy K, Ju G, Staines WA, Holets V, Schalling M, Ungerstedt U, Post C, Rehfeld JF, et al. Immunohistochemical studies on cholecystokinin (CCK)-immunoreactive neurons in the rat using sequence specific antisera and with special reference to the caudate nucleus and primary sensory neurons. *J Chem Neuroanat* 1: 11–51, 1988.

450. Holder JL Jr, Butte NF, Zinn AR. Profound obesity associated with a balanced translocation that disrupts the SIM1 gene. *Hum Mol Genet* 9: 101–108, 2000. doi:10.1093/hmg/9.1.101.

451. Hollis F, Sevelinges Y, Grosse J, Zanoletti O, Sandi C. Involvement of CRFR1 in the basolateral amygdala in the immediate fear extinction deficit. *eNeuro* 3: ENEURO.0084, 2016. doi:10.1523/ENEURO.0084-16.2016.

452. Holt-Lunstad J, Birmingham W, Light KC. The influence of depressive symptomatology and perceived stress on plasma and salivary oxytocin before, during and after a support enhancement intervention. *Psychoneuroendocrinology* 36: 1249–1256, 2011. doi:10.1016/j.psyneuen.2011.03.007.

453. Honda K, Sudo A, Ikeda K. Oxytocin cells in the supraoptic nucleus receive excitatory synaptic inputs from the contralateral supraoptic and paraventricular nuclei in the lactating rat. *J Reprod Dev* 59: 569–574, 2013. doi:10.1262/jrd.2013-053.

454. Hou C, Liu J, Wang K, Li L, Liang M, He Z, Liu Y, Zhang Y, Li W, Jiang T. Brain responses to symptom provocation and trauma-related short-term memory recall in coal mining accident survivors with acute severe PTSD. *Brain Res* 1144: 165–174, 2007. doi:10.1016/j.brainres.2007.01.089.

455. Hovey D, Lindstedt M, Zettergren A, Jonsson L, Johansson A, Melke J, Kerekes N, Anckarsäter H, Lichtenstein P, Lundström S, Westberg L. Antisocial behavior and polymorphisms in the oxytocin receptor gene: findings in two independent samples. *Mol Psychiatry* 21: 983–988, 2016. doi:10.1038/mp.2015.144.

456. Howell WH. The physiological effects of extracts of the hypophysis cerebri and infundibular body. *J Exp Med* 3: 245–258, 1898. doi:10.1084/jem.3.2.245.

457. Hoyle CH. Neuropeptide families and their receptors: evolutionary perspectives. *Brain Res* 848: 1–25, 1999. doi:10.1016/S0006-8993(99)01975-7.

458. Hrabovszky E, Csapó AK, Kalló I, Wilheim T, Túri GF, Liposits Z. Localization and osmotic regulation of vesicular glutamate transporter-2 in magnocellular neurons of the rat hypothalamus. *Neurochem Int* 48: 753–761, 2006. doi:10.1016/j.neuint.2005.12.013.

459. Hu J, Qi S, Becker B, Luo L, Gao S, Gong Q, Hurlemann R, Kendrick KM. Oxytocin selectively facilitates learning with social feedback and increases activity and functional connectivity in emotional memory and reward processing regions. *Hum Brain Mapp* 36: 2132–2146, 2015. doi:10.1002/hbm.22760.

460. Huang H, Michetti C, Busnelli M, Managò F, Sannino S, Scheggia D, Giancardo L, Sona D, Murino V, Chini B, Scattoni ML, Papaleo F. Chronic and acute intranasal oxytocin produce divergent social effects in mice. *Neuropsychopharmacology* 39: 1102–1114, 2014. doi:10.1038/npp.2013.310.

461. Huang WC, Ferris E, Cheng T, Hörndli CS, Gleason K, Tamminga C, Wagner JD, Boucher KM, Christian JL, Gregg C. Diverse non-genetic, allele-specific expression effects shape genetic architecture at the cellular level in the mammalian brain. *Neuron* 93: 1094–1109.e7, 2017. doi:10.1016/j.neuron.2017.01.033.

462. Huber D, Veinante P, Stoop R. Vasopressin and oxytocin excite distinct neuronal populations in the central amygdala. *Science* 308: 245–248, 2005. doi:10.1126/science.1105636.

463. Humerick M, Hanson J, Rodriguez-Canales J, Lubelski D, Rashid OM, Salinas YD, Shi Y, Ponzio T, Fields R, Emmert-Buck MR, Gainer H. Analysis of transcription factor mRNAs in identified oxytocin and vasopressin magnocellular neurons isolated by laser capture microdissection. *PLoS One* 8: e69407, 2013. doi:10.1371/journal.pone.0069407.

464. Hurlemann R, Patin A, Onur OA, Cohen MX, Baumgartner T, Metzler S, Dziobek I, Gallinat J, Wagner M, Maier W, Kendrick KM. Oxytocin enhances amygdala-dependent, socially reinforced learning and emotional empathy in humans. *J Neurosci* 30: 4999–5007, 2010. doi:10.1523/JNEUROSCI.5538-09.2010.

465. Hurlemann R, Scheele D. Dissecting the role of oxytocin in the formation and loss of social relationships. *Biol Psychiatry* 79: 185–193, 2016. doi:10.1016/j.biopsych.2015.05.013.

466. Ibragimov RS. Influence of neurohypophyseal peptides on the formation of active avoidance conditioned reflex behavior. *Neurosci Behav Physiol* 20: 189–193, 1990. doi:10.1007/BF01195453.

467. Im JY, Yoon SH, Kim BK, Ban HS, Won KJ, Chung KS, Jung KE, Won M. DNA damage induced apoptosis suppressor (DDIAS) is upregulated via ERK5/MEF2B signaling and promotes β-catenin-mediated invasion. *Biochim Biophys Acta* 1859: 1449–1458, 2016. doi:10.1016/j.bbagrm.2016.07.003.

468. Inenaga K, Yamashita H. Excitation of neurones in the rat paraventricular nucleus in vitro by vasopressin and oxytocin. *J Physiol* 370: 165–180, 1986. doi:10.1113/jphysiol.1986.sp015928.

469. Innamorati G, Giannone F, Guzzi F, Rovati GE, Accomazzo MR, Chini B, Bianchi E, Schiaffino MV, Tridente G, Parenti M. Heterotrimeric G proteins demonstrate differential sensitivity to beta-arrestin dependent desensitization. *Cell Signal* 21: 1135–1142, 2009. doi:10.1016/j.cellsig.2009.03.002.

470. Inoue T, Kimura T, Azuma C, Inazawa J, Takemura M, Kikuchi T, Kubota Y, Ogita K, Saji F. Structural organization of the human oxytocin receptor gene. *J Biol Chem* 269: 32451–32456, 1994.

471. Insel TR. Is social attachment an addictive disorder? *Physiol Behav* 79: 351–357, 2003. doi:10.1016/S0031-9384(03)00148-3.

472. Insel TR. Postpartum increases in brain oxytocin binding. *Neuroendocrinology* 44: 515–518, 1986. doi:10.1159/000124694.

473. Insel TR, Gelhard R, Shapiro LE. The comparative distribution of forebrain receptors for neurohypophyseal peptides in monogamous and polygamous mice. *Neuroscience* 43: 623–630, 1991. doi:10.1016/0306-4522(91)90321-E.

474. Insel TR, Harbaugh CR. Lesions of the hypothalamic paraventricular nucleus disrupt the initiation of maternal behavior. *Physiol Behav* 45: 1033–1041, 1989. doi:10.1016/0031-9384(89)90234-5.

475. Insel TR, Shapiro LE. Oxytocin receptor distribution reflects social organization in monogamous and polygamous voles. *Proc Natl Acad Sci USA* 89: 5981–5985, 1992. doi:10.1073/pnas.89.13.5981.

476. Insel TR, Wang ZX, Ferris CF. Patterns of brain vasopressin receptor distribution associated with social organization in microtine rodents. *J Neurosci* 14: 5381–5392, 1994.

477. Insel TR, Winslow JT, Wang ZX, Young L, Hulihan TJ. Oxytocin and the molecular basis of monogamy. *Adv Exp Med Biol* 395: 227–234, 1995.

478. Ishibashi M, Gumenchuk I, Miyazaki K, Inoue T, Ross WN, Leonard CS. Hypocretin/orexin peptides alter spike encoding by serotonergic dorsal raphe neurons through two distinct mechanisms that increase the late after hyperpolarization. *J Neurosci* 36: 10097–10115, 2016. doi:10.1523/JNEUROSCI.0635-16.2016.

479. Israel S, Lerer E, Shalev I, Uzefovsky F, Riebold M, Laiba E, Bachner-Melman R, Maril A, Bornstein G, Knafo A, Ebstein RP. The oxytocin receptor (OXTR) contributes to prosocial fund allocations in the dictator game and the social value orientations task. *PLoS One* 4: e5535, 2009. doi:10.1371/journal.pone.0005535.

480. Ivell R. Biosynthesis of oxytocin in the brain and peripheral organs. In: *Neurobiology of Oxytocin*, edited by Ganten D, Pfaff D. Berlin, Heidelberg: Springer Berlin Heidelberg, 1986, p. 1–18. doi:10.1007/978-3-642-70414-7_1.

481. Ivell R, Richter D. Structure and comparison of the oxytocin and vasopressin genes from rat. *Proc Natl Acad Sci USA* 81: 2006–2010, 1984. doi:10.1073/pnas.81.7.2006.

482. Iwasaki Y, Maejima Y, Suyama S, Yoshida M, Arai T, Katsurada K, Kumari P, Nakabayashi H, Kakei M, Yada T. Peripheral oxytocin activates vagal afferent neurons to suppress feeding in normal and leptin-resistant mice: a route for ameliorating hyperphagia and obesity. *Am J Physiol Regul Integr Comp Physiol* 308: R360–R369, 2015. doi:10.1152/ajpregu.00344.2014.

483. Jahn R, Scheller RH. SNAREs—engines for membrane fusion. *Nat Rev Mol Cell Biol* 7: 631–643, 2006. doi:10.1038/nrm2002.

484. Jahn R, Südhof TC. Synaptic vesicles and exocytosis. *Annu Rev Neurosci* 17: 219–246, 1994. doi:10.1146/annurev.ne.17.030194.001251.

485. Jain P, Lavorgna A, Sehgal M, Gao L, Ginwala R, Sagar D, Harhaj EW, Khan ZK. Myocyte enhancer factor (MEF)-2 plays essential roles in T-cell transformation associated with HTLV-1 infection by stabilizing complex between Tax and CREB. *Retrovirology* 12: 23, 2015. doi:10.1186/s12977-015-0140-1.

486. Jameson H, Bateman R, Byrne P, Dyavanapalli J, Wang X, Jain V, Mendelowitz D. Oxytocin neuron activation prevents hypertension that occurs with chronic intermittent hypoxia/hypercapnia in rats. *Am J Physiol Heart Circ Physiol* 310: H1549–H1557, 2016. doi:10.1152/ajpheart.00808.2015.

487. Jezova D, Skultetyova I, Tokarev DI, Bakos P, Vigas M. Vasopressin and oxytocin in stress. *Ann N Y Acad Sci* 771: 192–203, 1995. doi:10.1111/j.1749-6632.1995.tb44681.x.

488. Jiménez A, Young LJ, Triana-Del Río R, LaPrairie JL, González-Mariscal G. Neuroanatomical distribution of oxytocin receptor binding in the female rabbit forebrain: Variations across the reproductive cycle. *Brain Res* 1629: 329–339, 2015. doi:10.1016/j.brainres.2015.10.043.

489. Jin D, Liu HX, Hirai H, Torashima T, Nagai T, Lopatina O, Shnayder NA, Yamada K, Noda M, Seike T, Fujita K, Takasawa S, Yokoyama S, Koizumi K, Shiraishi Y, Tanaka S, Hashii M, Yoshihara T, Higashida K, Islam MS, Yamada N, Hayashi K, Noguchi N, Kato I, Okamoto H, Matsushima A, Salmina A, Munesue T, Shimizu N, Mochida S, Asano M, Higashida H. CD38 is critical for social behaviour by regulating oxytocin secretion. *Nature* 446: 41–45, 2007. doi:10.1038/nature05526.

490. Jo C, Cho SJ, Jo SA. Mitogen-activated protein kinase kinase 1 (MEK1) stabilizes MyoD through direct phosphorylation at tyrosine 156 during myogenic differentiation. *J Biol Chem* 286: 18903–18913, 2011. doi:10.1074/jbc.M111.225128.

491. Johansson A, Bergman H, Corander J, Waldman ID, Karrani N, Salo B, Jern P, Algars M, Sandnabba K, Santtila P, Westberg L. Alcohol and aggressive behavior in men–moderating effects of oxytocin receptor gene (OXTR) polymorphisms. *Genes Brain Behav* 11: 214–221, 2012. doi:10.1111/j.1601-183X.2011.00744.x.

492. Johansson A, Westberg L, Sandnabba K, Jern P, Salo B, Santtila P. Associations between oxytocin receptor gene (OXTR) polymorphisms and self-reported aggressive behavior and anger: Interactions with alcohol consumption. *Psychoneuroendocrinology* 37: 1546–1556, 2012. doi:10.1016/j.psyneuen.2012.02.009.

493. Johnson AE, Coirini H, Insel TR, McEwen BS. The regulation of oxytocin receptor binding in the ventromedial hypothalamic nucleus by testosterone and its metabolites. *Endocrinology* 128: 891–896, 1991. doi:10.1210/endo-128-2-891.

494. Johnson ZV, Walum H, Jamal YA, Xiao Y, Keebaugh AC, Inoue K, Young LJ. Central oxytocin receptors mediate mating-induced partner preferences and enhance correlated activation across forebrain nuclei in male prairie voles. *Horm Behav* 79: 8–17, 2016. doi:10.1016/j.yhbeh.2015.11.011.

495. Johnstone LE, Fong TM, Leng G. Neuronal activation in the hypothalamus and brainstem during feeding in rats. *Cell Metab* 4: 313–321, 2006. doi:10.1016/j.cmet.2006.08.003.

496. Jokinen J, Chatzittofis A, Hellström C, Nordström P, Uvnäs-Moberg K, Asberg M. Low CSF oxytocin reflects high intent in suicide attempters. *Psychoneuroendocrinology* 37: 482–490, 2012. doi:10.1016/j.psyneuen.2011.07.016.

497. Jørgensen H, Riis M, Knigge U, Kjaer A, Warberg J. Serotonin receptors involved in vasopressin and oxytocin secretion. *J Neuroendocrinol* 15: 242–249, 2003. doi:10.1046/j.1365-2826.2003.00978.x.

498. Joux N, Chevaleyre V, Alonso G, Boissin-Agasse L, Moos FC, Desarménien MG, Hussy N. High voltage-activated Ca2+ currents in rat supraoptic neurones: biophysical properties and expression of the various channel alpha1 subunits. *J Neuroendocrinol* 13: 638–649, 2001. doi:10.1046/j.1365-2826.2001.00679.x.

499. Jurek B, Slattery DA, Hiraoka Y, Liu Y, Nishimori K, Aguilera G, Neumann ID, van den Burg EH. Oxytocin regulates stress-induced Crf gene transcription through CREB-regulated transcription coactivator 3. *J Neurosci* 35: 12248–12260, 2015. doi:10.1523/JNEUROSCI.1345-14.2015.

500. Jurek B, Slattery DA, Maloumby R, Hillerer K, Koszinowski S, Neumann ID, van den Burg EH. Differential contribution of hypothalamic MAPK activity to anxiety-like behaviour in virgin and lactating rats. *PLoS One* 7: e37060, 2012. doi:10.1371/journal.pone.0037060.

501. Kaba H, Nakanishi S. Synaptic mechanisms of olfactory recognition memory. *Rev Neurosci* 6: 125–141, 1995. doi:10.1515/REVNEURO.1995.6.2.125.

502. Kagerbauer SM, Martin J, Schuster T, Blobner M, Kochs EF, Landgraf R. Plasma oxytocin and vasopressin do not predict neuropeptide concentrations in human cerebrospinal fluid. *J Neuroendocrinol* 25: 668–673, 2013. doi:10.1111/jne.12038.

503. Kageyama K, Suda T. Regulatory mechanisms underlying corticotropin-releasing factor gene expression in the hypothalamus. *Endocr J* 56: 335–344, 2009. doi:10.1507/endocrj.K09E-075.

504. Kalsbeek A, Buijs RM, Engelmann M, Wotjak CT, Landgraf R. In vivo measurement of a diurnal variation in vasopressin release in the rat suprachiasmatic nucleus. *Brain Res* 682: 75–82, 1995. doi:10.1016/0006-8993(95)00324-J.

505. Kamm O. The dialysis of pituitary extracts. *Science* 67: 199–200, 1928. doi:10.1126/science.67.1729.199.

506. Kanat M, Heinrichs M, Schwarzwald R, Domes G. Oxytocin attenuates neural reactivity to masked threat cues from the eyes. *Neuropsychopharmacology* 40: 287–295, 2015. doi:10.1038/npp.2014.183.

507. Kang H, Schuman EM. A requirement for local protein synthesis in neurotrophin-induced hippocampal synaptic plasticity. *Science* 273: 1402–1406, 1996.

508. Karpova IV, Mikheev VV, Marysheva VV, Bychkov ER, Proshin SN. Oxytocin-induced changes in monoamine level in symmetric brain structures of isolated aggressive C57Bl/6 mice. *Bull Exp Biol Med* 160: 605–609, 2016. doi:10.1007/s10517-016-3228-2.

509. Kasting NW. Simultaneous and independent release of vasopressin and oxytocin in the rat. *Can J Physiol Pharmacol* 66: 22–26, 1988. doi:10.1139/y88-004.

510. Kawata M, Sano Y. Immunohistochemical identification of the oxytocin and vasopressin neurons in the hypothalamus of the monkey (*Macaca fuscata*). *Anat Embryol (Berl)* 165: 151–167, 1982. doi:10.1007/BF00305474.

511. Keating C, Dawood T, Barton DA, Lambert GW, Tilbrook AJ. Effects of selective serotonin reuptake inhibitor treatment on plasma oxytocin and cortisol in major depressive disorder. *BMC Psychiatry* 13: 124, 2013. doi:10.1186/1471-244X-13-124.

512. Keck ME. Corticotropin-releasing factor, vasopressin and receptor systems in depression and anxiety. *Amino Acids* 31: 241–250, 2006. doi:10.1007/s00726-006-0333-y.

513. Keebaugh AC, Barrett CE, Laprairie JL, Jenkins JJ, Young LJ. RNAi knockdown of oxytocin receptor in the nucleus accumbens inhibits social attachment and parental care in monogamous female prairie voles. *Soc Neurosci* 10: 561–570, 2015. doi:10.1080/17470919.2015.1040893.

514. Kelly AM, Goodson JL. Hypothalamic oxytocin and vasopressin neurons exert sex-specific effects on pair bonding, gregariousness, and aggression in finches. *Proc Natl Acad Sci USA* 111: 6069–6074, 2014. doi:10.1073/pnas.1322554111.

515. Kemp AH, Quintana DS, Kuhnert RL, Griffiths K, Hickie IB, Guastella AJ. Oxytocin increases heart rate variability in humans at rest: implications for social approach-related motivation and capacity for social engagement. *PLoS One* 7: e44014, 2012. doi:10.1371/journal.pone.0044014.

516. Kendrick KM, Da Costa AP, Broad KD, Ohkura S, Guevara R, Lévy F, Keverne EB. Neural control of maternal behaviour and olfactory recognition of offspring. *Brain Res Bull* 44: 383–395, 1997. doi:10.1016/S0361-9230(97)00218-9.

517. Kendrick KM, Keverne EB, Chapman C, Baldwin BA. Intracranial dialysis measurement of oxytocin, monoamine and uric acid release from the olfactory bulb and substantia nigra of sheep during parturition, suckling, separation from lambs and eating. *Brain Res* 439: 1–10, 1988. doi:10.1016/0006-8993(88)91455-2.

518. Kendrick KM, Keverne EB, Chapman C, Baldwin BA. Microdialysis measurement of oxytocin, aspartate, gamma-aminobutyric acid and glutamate release from the olfactory bulb of the sheep during vaginocervical stimulation. *Brain Res* 442: 171–174, 1988. doi:10.1016/0006-8993(88)91447-3.

519. Kendrick KM, Keverne EB, Hinton MR, Goode JA. Cerebrospinal fluid and plasma concentrations of oxytocin and vasopressin during parturition and vaginocervical stimulation in the sheep. *Brain Res Bull* 26: 803–807, 1991. doi:10.1016/0361-9230(91)90178-M.

520. Kendrick KM, Keverne EB, Hinton MR, Goode JA. Oxytocin, amino acid and monoamine release in the region of the medial preoptic area and bed nucleus of the stria terminalis of the sheep during parturition and suckling. *Brain Res* 569: 199–209, 1992. doi:10.1016/0006-8993(92)90631-I.

521. Kennedy SH. Core symptoms of major depressive disorder: relevance to diagnosis and treatment. *Dialogues Clin Neurosci* 10: 271–277, 2008.

522. Kessler RC, Aguilar-Gaxiola S, Alonso J, Chatterji S, Lee S, Ormel J, Ustün TB, Wang PS. The global burden of mental disorders: an update from the WHO World Mental Health (WMH) surveys. *Epidemiol Psichiatr Soc* 18: 23–33, 2009. doi:10.1017/S1121189X00001421.

523. Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int J Methods Psychiatr Res* 21: 169–184, 2012. doi:10.1002/mpr.1359.

524. Keverne EB, Brennan PA. Olfactory recognition memory. *J Physiol Paris* 90: 399–401, 1996. doi:10.1016/S0928-4257(97)87929-6.

525. Keverne EB, de la Riva C. Pheromones in mice: reciprocal interaction between the nose and brain. *Nature* 296: 148–150, 1982. doi:10.1038/296148a0.

526. Khalil R, Fendt M. Increased anxiety but normal fear and safety learning in orexin-deficient mice. *Behav Brain Res* 320: 210–218, 2017. doi:10.1016/j.bbr.2016.12.007.

527. Kim HS, Sherman DK, Sasaki JY, Xu J, Chu TQ, Ryu C, Suh EM, Graham K, Taylor SE. Culture, distress, and oxytocin receptor polymorphism (OXTR) interact to influence emotional support seeking. *Proc Natl Acad Sci USA* 107: 15717–15721, 2010. doi:10.1073/pnas.1010830107.

528. Kim SH, MacIntyre DA, Firmino Da Silva M, Blanks AM, Lee YS, Thornton S, Bennett PR, Terzidou V. Oxytocin activates NF-κB-mediated inflammatory pathways in human gestational tissues. *Mol Cell Endocrinol* 403: 64–77, 2015. doi:10.1016/j.mce.2014.11.008.

530. Kim SH, Pohl O, Chollet A, Gotteland JP, Fairhurst AD, Bennett PR, Terzidou V. Differential effects of oxytocin receptor antagonists, Atosiban and Nolasiban, on OT-mediated signalling in human amnion and myometrium. *Mol Pharmacol* 91: 403–415, 2017. doi:10.1124/mol.116.106013.

531. Kim Y, Park MK, Chung S. Regulation of somatodendritic dopamine release by corticotropin-releasing factor via the inhibition of voltage-operated Ca2+ channels. *Neurosci Lett* 465: 31–35, 2009. doi:10.1016/j.neulet.2009.08.066.

532. Kimura T, Ito Y, Einspanier A, Tohya K, Nobunaga T, Tokugawa Y, Takemura M, Kubota Y, Ivell R, Matsuura N, Saji F, Murata Y. Expression and immunolocalization of the oxytocin receptor in human lactating and non-lactating mammary glands. *Hum Reprod* 13: 2645–2653, 1998. doi:10.1093/humrep/13.9.2645.

533. Kimura T, Ogita K, Kumasawa K, Tomimatsu T, Tsutsui T. Molecular analysis of parturition via oxytocin receptor expression. *Taiwan J Obstet Gynecol* 52: 165–170, 2013. doi:10.1016/j.tjog.2013.04.004.

534. Kimura T, Saji F, Nishimori K, Ogita K, Nakamura H, Koyama M, Murata Y. Molecular regulation of the oxytocin receptor in peripheral organs. *J Mol Endocrinol* 30: 109–115, 2003. doi:10.1677/jme.0.0300109.

535. Kimura T, Tanizawa O, Mori K, Brownstein MJ, Okayama H. Structure and expression of a human oxytocin receptor. *Nature* 356: 526–529, 1992. doi:10.1038/356526a0.

536. Kirchgessner AL, Sclafani A. PVN-hindbrain pathway involved in the hypothalamic hyperphagia-obesity syndrome. *Physiol Behav* 42: 517–528, 1988. doi:10.1016/0031-9384(88)90153-9.

537. Kirsch P, Esslinger C, Chen Q, Mier D, Lis S, Siddhanti S, Gruppe H, Mattay VS, Gallhofer B, Meyer-Lindenberg A. Oxytocin modulates neural circuitry for social cognition and fear in humans. *J Neurosci* 25: 11489–11493, 2005. doi:10.1523/JNEUROSCI.3984-05.2005.

538. Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test'–a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology* 28: 76–81, 1993. doi:10.1159/000119004.

539. Kita I, Yoshida Y, Nishino S. An activation of parvocellular oxytocinergic neurons in the paraventricular nucleus in oxytocin-induced yawning and penile erection. *Neurosci Res* 54: 269–275, 2006. doi:10.1016/j.neures.2005.12.005.

540. Klampfl SM, Neumann ID, Bosch OJ. Reduced brain corticotropin-releasing factor receptor activation is required for adequate maternal care and maternal aggression in lactating rats. *Eur J Neurosci* 38: 2742–2750, 2013. doi:10.1111/ejn.12274.

541. Klatt JD, Goodson JL. Oxytocin-like receptors mediate pair bonding in a socially monogamous songbird. *Proc Biol Sci* 280: 20122396, 2013. doi:10.1098/rspb.2012.2396.

542. Klein BY, Tamir H, Hirschberg DL, Glickstein SB, Welch MG. Oxytocin modulates mTORC1 pathway in the gut. *Biochem Biophys Res Commun* 432: 466–471, 2013. doi:10.1016/j.bbrc.2013.01.121.

543. Klemke M, Kramer E, Konstandin MH, Wabnitz GH, Samstag Y. An MEK-cofilin signalling module controls migration of human T cells in 3D but not 2D environments. *EMBO J* 29: 2915–2929, 2010. doi:10.1038/emboj.2010.153.

544. Knobloch HS, Charlet A, Hoffmann LC, Eliava M, Khrulev S, Cetin AH, Osten P, Schwarz MK, Seeburg PH, Stoop R, Grinevich V. Evoked axonal oxytocin release in the central amygdala attenuates fear response. *Neuron* 73: 553–566, 2012. doi:10.1016/j.neuron.2011.11.030.

545. Knobloch HS, Grinevich V. Evolution of oxytocin pathways in the brain of vertebrates. *Front Behav Neurosci* 8: 31, 2014. doi:10.3389/fnbeh.2014.00031.

547. Kogan A, Saslow LR, Impett EA, Oveis C, Keltner D, Rodrigues Saturn S. Thin-slicing study of the oxytocin receptor (OXTR) gene and the evaluation and expression of the prosocial disposition. *Proc Natl Acad Sci USA* 108: 19189–19192, 2011. doi:10.1073/pnas.1112658108.

548. Komisaruk BR, Sansone G. Neural pathways mediating vaginal function: the vagus nerves and spinal cord oxytocin. *Scand J Psychol* 44: 241–250, 2003. doi:10.1111/1467-9450.00341.

549. Komisaruk BR, Whipple B. Functional MRI of the brain during orgasm in women. *Annu Rev Sex Res* 16: 62–86, 2005.

550. Komisaruk BR, Whipple B, Crawford A, Liu WC, Kalnin A, Mosier K. Brain activation during vaginocervical self-stimulation and orgasm in women with complete spinal cord injury: fMRI evidence of mediation by the vagus nerves. *Brain Res* 1024: 77–88, 2004. doi:10.1016/j.brainres.2004.07.029.

551. Koob GF, Sanna PP, Bloom FE. Neuroscience of addiction. *Neuron* 21: 467–476, 1998. doi:10.1016/S0896-6273(00)80557-7.

552. Koob GF, Volkow ND. Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry* 3: 760–773, 2016. doi:10.1016/S2215-0366(16)00104-8.

553. Koolhaas JM, Coppens CM, de Boer SF, Buwalda B, Meerlo P, Timmermans PJ. The resident-intruder paradigm: a standardized test for aggression, violence and social stress. *J Vis Exp* 2013: e4367, 2013.

554. Kosfeld M, Heinrichs M, Zak PJ, Fischbacher U, Fehr E. Oxytocin increases trust in humans. *Nature* 435: 673–676, 2005. doi:10.1038/nature03701.

555. Kovács GL, Bohus B, Versteeg DH, de Kloet ER, de Wied D. Effect of oxytocin and vasopressin on memory consolidation: sites of action and catecholaminergic correlates after local microinjection into limbic-midbrain structures. *Brain Res* 175: 303–314, 1979. doi:10.1016/0006-8993(79)91009-6.

556. Kovács GL, Borthaiser Z, Telegdy G. Oxytocin reduces intravenous heroin self-administration in heroin-tolerant rats. *Life Sci* 37: 17–26, 1985. doi:10.1016/0024-3205(85)90620-4.

557. Kovács GL, Faludi M, Telegdy G. Oxytocin diminishes heroin tolerance in mice. *Psychopharmacology (Berl)* 86: 377–379, 1985. doi:10.1007/BF00432233.

558. Kovàcs GL, Sarnyai Z, Barbarczi E, Szabó G, Telegdy G. The role of oxytocin-dopamine interactions in cocaine-induced locomotor hyperactivity. *Neuropharmacology* 29: 365–368, 1990. doi:10.1016/0028-3908(90)90095-9.

559. Kovács GL, Sarnyai Z, Szabó G. Oxytocin and addiction: a review. *Psychoneuroendocrinology* 23: 945–962, 1998. doi:10.1016/S0306-4530(98)00064-X.

560. Kovács GL, Telegdy G. Role of oxytocin in memory and amnesia. *Pharmacol Ther* 18: 375–395, 1982. doi:10.1016/0163-7258(82)90038-9.

561. Kovács KA, Steullet P, Steinmann M, Do KQ, Magistretti PJ, Halfon O, Cardinaux JR. TORC1 is a calcium- and cAMP-sensitive coincidence detector involved in hippocampal long-term synaptic plasticity. *Proc Natl Acad Sci USA* 104: 4700–4705, 2007. doi:10.1073/pnas.0607524104.

562. Kranz TM, Kopp M, Waltes R, Sachse M, Duketis E, Jarczok TA, Degenhardt F, Görgen K, Meyer J, Freitag CM, Chiocchetti AG. Meta-analysis and association of two common polymorphisms of the human oxytocin receptor gene in autism spectrum disorder. *Autism Res* 9: 1036–1045, 2016. doi:10.1002/aur.1597.

563. Krishnaswamy N, Lacroix-Pepin N, Chapdelaine P, Taniguchi H, Kauffenstein G, Chakravarti A, Danyod G, Fortier MA. Epidermal growth factor receptor is an obligatory intermediate for oxytocin-induced cyclooxygenase 2 expression and prostaglandin F2 alpha production in bovine endometrial epithelial cells. *Endocrinology* 151: 1367–1374, 2010. doi:10.1210/en.2009-1304.

564. Kroll-Desrosiers AR, Nephew BC, Babb JA, Guilarte-Walker Y, Moore Simas TA, Deligiannidis KM. Association of peripartum synthetic oxytocin administration and depressive and anxiety disorders within the first postpartum year. *Depress Anxiety* 34: 137–146, 2017. doi:10.1002/da.22599.

565. Krüger TH, Haake P, Chereath D, Knapp W, Janssen OE, Exton MS, Schedlowski M, Hartmann U. Specificity of the neuroendocrine response to orgasm during sexual arousal in men. *J Endocrinol* 177: 57–64, 2003. doi:10.1677/joe.0.1770057.

566. Krüger TH, Schiffer B, Eikermann M, Haake P, Gizewski E, Schedlowski M. Serial neurochemical measurement of cerebrospinal fluid during the human sexual response cycle. *Eur J Neurosci* 24: 3445–3452, 2006. doi:10.1111/j.1460-9568.2006.05215.x.

567. Ku CY, Qian A, Wen Y, Anwer K, Sanborn BM. Oxytocin stimulates myometrial guanosine triphosphatase and phospholipase-C activities via coupling to G alpha q/11. *Endocrinology* 136: 1509–1515, 1995. doi:10.1210/endo.136.4.7895660.

568. Kubes M, Cordier J, Glowinski J, Girault JA, Chneiweiss H. Endothelin induces a calcium-dependent phosphorylation of PEA-15 in intact astrocytes: identification of Ser104 and Ser116 phosphorylated, respectively, by protein kinase C and calcium/calmodulin kinase II in vitro. *J Neurochem* 71: 1307–1314, 1998. doi:10.1046/j.1471-4159.1998.71031307.x.

569. Kublaoui BM, Gemelli T, Tolson KP, Wang Y, Zinn AR. Oxytocin deficiency mediates hyperphagic obesity of Sim1 haploinsufficient mice. *Mol Endocrinol* 22: 1723–1734, 2008. doi:10.1210/me.2008-0067.

570. Kublaoui BM, Holder JL Jr, Tolson KP, Gemelli T, Zinn AR. SIM1 overexpression partially rescues agouti yellow and diet-induced obesity by normalizing food intake. *Endocrinology* 147: 4542–4549, 2006. doi:10.1210/en.2006-0453.

571. Kubota Y, Kimura T, Hashimoto K, Tokugawa Y, Nobunaga K, Azuma C, Saji F, Murata Y. Structure and expression of the mouse oxytocin receptor gene. *Mol Cell Endocrinol* 124: 25–32, 1996. doi:10.1016/S0303-7207(96)03923-8.

572. Kumar A, Singh N. Calcineurin inhibitors improve memory loss and neuropathological changes in mouse model of dementia. *Pharmacol Biochem Behav* 153: 147–159, 2017. doi:10.1016/j.pbb.2016.12.018.

573. Kusui C, Kimura T, Ogita K, Nakamura H, Matsumura Y, Koyama M, Azuma C, Murata Y. DNA methylation of the human oxytocin receptor gene promoter regulates tissue-specific gene suppression. *Biochem Biophys Res Commun* 289: 681–686, 2001. doi:10.1006/bbrc.2001.6024.

574. Kutlu S, Aydin M, Alcin E, Ozcan M, Bakos J, Jezova D, Yilmaz B. Leptin modulates noradrenaline release in the paraventricular nucleus and plasma oxytocin levels in female rats: a microdialysis study. *Brain Res* 1317: 87–91, 2010. doi:10.1016/j.brainres.2009.12.044.

575. Kyriakis JM, Avruch J. Mammalian MAPK signal transduction pathways activated by stress and inflammation: a 10-year update. *Physiol Rev* 92: 689–737, 2012. doi:10.1152/physrev.00028.2011.

576. Labuschagne I, Phan KL, Wood A, Angstadt M, Chua P, Heinrichs M, Stout JC, Nathan PJ. Oxytocin attenuates amygdala reactivity to fear in generalized social anxiety disorder. *Neuropsychopharmacology* 35: 2403–2413, 2010. doi:10.1038/npp.2010.123.

577. Lagman D, Ocampo Daza D, Widmark J, Abalo XM, Sundström G, Larhammar D. The vertebrate ancestral repertoire of visual opsins, transducin alpha subunits and oxytocin/vasopressin receptors was established by duplication of their shared genomic region in the two rounds of early vertebrate genome duplications. *BMC Evol Biol* 13: 238, 2013. doi:10.1186/1471-2148-13-238.

578. Laguna-Abreu MT, Margatho L, Germano CM, Antunes-Rodrigues J, Elias LL, de Castro M. The effect of adrenalectomy on Fos expression in vasopressinergic and oxytocinergic neurons in response to stress in the rat. *Stress* 10: 332–341, 2007. doi:10.1080/10253890701287614.

579. Lahoud N, Maroun M. Oxytocinergic manipulations in corticolimbic circuit differentially affect fear acquisition and extinction. *Psychoneuroendocrinology* 38: 2184–2195, 2013. doi:10.1016/j.psyneuen.2013.04.006.

580. Lambert RC, Dayanithi G, Moos FC, Richard P. A rise in the intracellular Ca2+ concentration of isolated rat supraoptic cells in response to oxytocin. *J Physiol* 478: 275–287, 1994. doi:10.1113/jphysiol.1994.sp020249.

581. Lambert RC, Moos FC, Richard P. Action of endogenous oxytocin within the paraventricular or supraoptic nuclei: a powerful link in the regulation of the bursting pattern of oxytocin neurons during the milk-ejection reflex in rats. *Neuroscience* 57: 1027–1038, 1993. doi:10.1016/0306-4522(93)90046-I.

582. Lancel M, Krömer S, Neumann ID. Intracerebral oxytocin modulates sleep-wake behaviour in male rats. *Regul Pept* 114: 145–152, 2003. doi:10.1016/S0167-0115(03)00118-6.

583. Landgraf R. Plasma oxytocin concentrations in man after different routes of administration of synthetic oxytocin. *Exp Clin Endocrinol* 85: 245–248, 1985. doi:10.1055/s-0029-1210444.

584. Landgraf R, Häcker R, Buhl H. Plasma vasopressin and oxytocin in response to exercise and during a day-night cycle in man. *Endokrinologie* 79: 281–291, 1982.

585. Landgraf R, Hess J, Ermisch A. The influence of vasopressin on the regional uptake of [3H] orotic acid by rat brain. *Acta Biol Med Ger* 37: 655–658, 1978.

586. Landgraf R, Ludwig M. Vasopressin release within the supraoptic and paraventricular nuclei of the rat brain: osmotic stimulation via microdialysis. *Brain Res* 558: 191–196, 1991. doi:10.1016/0006-8993(91)90768-Q.

587. Landgraf R, Malkinson T, Horn T, Veale WL, Lederis K, Pittman QJ. Release of vasopressin and oxytocin by paraventricular stimulation in rats. *Am J Physiol Regul Integr Comp Physiol* 258: R155–R159, 1990.

588. Landgraf R, Neumann I, Pittman QJ. Septal and hippocampal release of vasopressin and oxytocin during late pregnancy and parturition in the rat. *Neuroendocrinology* 54: 378–383, 1991. doi:10.1159/000125917.

589. Landgraf R, Neumann I, Russell JA, Pittman QJ. Push-pull perfusion and microdialysis studies of central oxytocin and vasopressin release in freely moving rats during pregnancy, parturition, and lactation. *Ann N Y Acad Sci* 652: 326–339, 1992. doi:10.1111/j.1749-6632.1992.tb34364.x.

590. Landgraf R, Neumann I, Schwarzberg H. Central and peripheral release of vasopressin and oxytocin in the conscious rat after osmotic stimulation. *Brain Res* 457: 219–225, 1988. doi:10.1016/0006-8993(88)90689-0.

591. Landgraf R, Neumann ID. Vasopressin and oxytocin release within the brain: a dynamic concept of multiple and variable modes of neuropeptide communication. *Front Neuroendocrinol* 25: 150–176, 2004. doi:10.1016/j.yfrne.2004.05.001.

592. Landgraf R, Schulz J, Eulenberger K, Wilhelm J. Plasma levels of oxytocin and vasopressin before, during and after parturition in cows. *Exp Clin Endocrinol* 81: 321–328, 1983. doi:10.1055/s-0029-1210243.

593. Lang RE, Heil JW, Ganten D, Hermann K, Unger T, Rascher W. Oxytocin unlike vasopressin is a stress hormone in the rat. *Neuroendocrinology* 37: 314–316, 1983. doi:10.1159/000123566.

594. Lawson EA, Holsen LM, Santin M, DeSanti R, Meenaghan E, Eddy KT, Herzog DB, Goldstein JM, Klibanski A. Postprandial oxytocin secretion is associated with severity of anxiety and depressive symptoms in anorexia nervosa. *J Clin Psychiatry* 74: e451–e457, 2013. doi:10.4088/JCP.12m08154.

595. Lawson SK, Gray AC, Woehrle NS. Effects of oxytocin on serotonin 1B agonist-induced autism-like behavior in mice. *Behav Brain Res* 314: 52–64, 2016. doi:10.1016/j.bbr.2016.07.027.

596. Lazzari VM, Becker RO, de Azevedo MS, Morris M, Rigatto K, Almeida S, Lucion AB, Giovenardi M. Oxytocin modulates social interaction but is not essential for sexual behavior in male mice. *Behav Brain Res* 244: 130–136, 2013. doi:10.1016/j.bbr.2013.01.025.

597. LeDoux JE, Iwata J, Cicchetti P, Reis DJ. Different projections of the central amygdaloid nucleus mediate autonomic and behavioral correlates of conditioned fear. *J Neurosci* 8: 2517–2529, 1988.

598. Lee AG, Cool DR, Grunwald WC Jr, Neal DE, Buckmaster CL, Cheng MY, Hyde SA, Lyons DM, Parker KJ. A novel form of oxytocin in New World monkeys. *Biol Lett* 7: 584–587, 2011. doi:10.1098/rsbl.2011.0107.

599. Lee ES, Uhm KO, Lee YM, Kwon J, Park SH, Soo KH. Oxytocin stimulates glucose uptake in skeletal muscle cells through the calcium-CaMKK-AMPK pathway. *Regul Pept* 151: 71–74, 2008. doi:10.1016/j.regpep.2008.05.001.

600. Lee HC. Nicotinic acid adenine dinucleotide phosphate (NAADP)-mediated calcium signaling. *J Biol Chem* 280: 33693–33696, 2005. doi:10.1074/jbc.R500012200.

601. Lee HJ, Caldwell HK, Macbeth AH, Tolu SG, Young WS III. A conditional knockout mouse line of the oxytocin receptor. *Endocrinology* 149: 3256–3263, 2008. doi:10.1210/en.2007-1710.

602. Lee MR, Weerts EM. Oxytocin for the treatment of drug and alcohol use disorders. *Behav Pharmacol* 27: 640–648, 2016. doi:10.1097/FBP.0000000000000258.

603. Lee R, Ferris C, Van de Kar LD, Coccaro EF. Cerebrospinal fluid oxytocin, life history of aggression, and personality disorder. *Psychoneuroendocrinology* 34: 1567–1573, 2009. doi:10.1016/j.psyneuen.2009.06.002.

604. Lefebvre DL, Giaid A, Bennett H, Larivière R, Zingg HH. Oxytocin gene expression in rat uterus. *Science* 256: 1553–1555, 1992. doi:10.1126/science.1598587.

605. Leibowitz SF, Hammer NJ, Chang K. Hypothalamic paraventricular nucleus lesions produce overeating and obesity in the rat. *Physiol Behav* 27: 1031–1040, 1981. doi:10.1016/0031-9384(81)90366-8.

606. Lema SC, Sanders KE, Walti KA. Arginine vasotocin, isotocin and nonapeptide receptor gene expression link to social status and aggression in sex-dependent patterns. *J Neuroendocrinol* 27: 142–157, 2015. doi:10.1111/jne.12239.

607. Leng G, Ludwig M. Intranasal Oxytocin: Myths and Delusions. *Biol Psychiatry* 79: 243–250, 2016. doi:10.1016/j.biopsych.2015.05.003.

608. Leng G, Ludwig M. Neurotransmitters and peptides: whispered secrets and public announcements. *J Physiol* 586: 5625–5632, 2008. doi:10.1113/jphysiol.2008.159103.

609. Leng G, Way S, Dyball RE. Identification of oxytoxin cells in the rat supraoptic nucleus by their response to cholecystokinin injection. *Neurosci Lett* 122: 159–162, 1991. doi:10.1016/0304-3940(91)90847-M.

610. Lestanova Z, Bacova Z, Kiss A, Havranek T, Strbak V, Bakos J. Oxytocin increases neurite length and expression of cytoskeletal proteins associated with neuronal growth. *J Mol Neurosci* 59: 184–192, 2016. doi:10.1007/s12031-015-0664-9.

611. Lestanova Z, Puerta F, Alanazi M, Bacova Z, Kiss A, Castejon AM, Bakos J. Down-regulation of oxytocin receptor decreases the length of projections stimulated by retinoic acid in the U-87MG cells. *Neurochem Res* 42: 1006–1014, 2017. doi:10.1007/s11064-016-2133-4.

612. Leuner B, Caponiti JM, Gould E. Oxytocin stimulates adult neurogenesis even under conditions of stress and elevated glucocorticoids. *Hippocampus* 22: 861–868, 2012. doi:10.1002/hipo.20947.

613. Leveque TF, Scharrer E. Pituicytes and the origin of the antidiuretic hormone. *Endocrinology* 52: 436–447, 1953. doi:10.1210/endo-52-4-436.

614. Levin ER. Extranuclear steroid receptors are essential for steroid hormone actions. *Annu Rev Med* 66: 271–280, 2015. doi:10.1146/annurev-med-050913-021703.

615. Levy T, Bloch Y, Bar-Maisels M, Gat-Yablonski G, Djalovski A, Borodkin K, Apter A. Salivary oxytocin in adolescents with conduct problems and callous-unemotional traits. *Eur Child Adolesc Psychiatry* 24: 1543–1551, 2015. doi:10.1007/s00787-015-0765-6.

616. Li K, Nakajima M, Ibañez-Tallon I, Heintz N. A cortical circuit for sexually dimorphic oxytocin-dependent anxiety behaviors. *Cell* 167: 60–72.e11, 2016. doi:10.1016/j.cell.2016.08.067.

617. Liberzon I, Chalmers DT, Mansour A, Lopez JF, Watson SJ, Young EA. Glucocorticoid regulation of hippocampal oxytocin receptor binding. *Brain Res* 650: 317–322, 1994. doi:10.1016/0006-8993(94)91798-1.

618. Liberzon I, Young EA. Effects of stress and glucocorticoids on CNS oxytocin receptor binding. *Psychoneuroendocrinology* 22: 411–422, 1997. doi:10.1016/S0306-4530(97)00045-0.

619. Lightman SL, Windle RJ, Wood SA, Kershaw YM, Shanks N, Ingram CD. Peripartum plasticity within the hypothalamo-pituitary-adrenal axis. *Prog Brain Res* 133: 111–129, 2001. doi:10.1016/S0079-6123(01)33009-1.

620. Lin CH, Yeh SH, Leu TH, Chang WC, Wang ST, Gean PW. Identification of calcineurin as a key signal in the extinction of fear memory. *J Neurosci* 23: 1574–1579, 2003.

621. Lin YT, Huang CC, Hsu KS. Oxytocin promotes long-term potentiation by enhancing epidermal growth factor receptor-mediated local translation of protein kinase Mζ. *J Neurosci* 32: 15476–15488, 2012. doi:10.1523/JNEUROSCI.2429-12.2012.

622. Lindvall O, Björklund A, Skagerberg G. Selective histochemical demonstration of dopamine terminal systems in rat di- and telencephalon: new evidence for dopaminergic innervation of hypothalamic neurosecretory nuclei. *Brain Res* 306: 19–30, 1984. doi:10.1016/0006-8993(84)90352-4.

623. Lischke A, Gamer M, Berger C, Grossmann A, Hauenstein K, Heinrichs M, Herpertz SC, Domes G. Oxytocin increases amygdala reactivity to threatening scenes in females. *Psychoneuroendocrinology* 37: 1431–1438, 2012. doi:10.1016/j.psyneuen.2012.01.011.

624. Litvin Y, Murakami G, Pfaff DW. Effects of chronic social defeat on behavioral and neural correlates of sociality: Vasopressin, oxytocin and the vasopressinergic V1b receptor. *Physiol Behav* 103: 393–403, 2011. doi:10.1016/j.physbeh.2011.03.007.

625. Liu Y, Coello AG, Grinevich V, Aguilera G. Involvement of transducer of regulated cAMP response element-binding protein activity on corticotropin releasing hormone transcription. *Endocrinology* 151: 1109–1118, 2010. doi:10.1210/en.2009-0963.

626. Liu Y, Knobloch HS, Grinevich V, Aguilera G. Stress induces parallel changes in corticotrophin-releasing hormone (CRH) transcription and nuclear translocation of transducer of regulated cAMP response element-binding activity 2 in hypothalamic CRH neurones. *J Neuroendocrinol* 23: 216–223, 2011. doi:10.1111/j.1365-2826.2010.02101.x.

627. Liu Y, Wang ZX. Nucleus accumbens oxytocin and dopamine interact to regulate pair bond formation in female prairie voles. *Neuroscience* 121: 537–544, 2003. doi:10.1016/S0306-4522(03)00555-4.

628. Liu YC, Salamone JD, Sachs BD. Impaired sexual response after lesions of the paraventricular nucleus of the hypothalamus in male rats. *Behav Neurosci* 111: 1361–1367, 1997. doi:10.1037/0735-7044.111.6.1361.

629. Liu YF, Bertram K, Perides G, McEwen BS, Wang D. Stress induces activation of stress-activated kinases in the mouse brain. *J Neurochem* 89: 1034–1043, 2004. doi:10.1111/j.1471-4159.2004.02391.x.

630. Lonstein JS, Maguire J, Meinlschmidt G, Neumann ID. Emotion and mood adaptations in the peripartum female:complementary contributions of GABA and oxytocin. *J Neuroendocrinol* 26: 649–664, 2014. doi:10.1111/jne.12188.

631. Lonstein JS, Stern JM. Site and behavioral specificity of periaqueductal gray lesions on postpartum sexual, maternal, and aggressive behaviors in rats. *Brain Res* 804: 21–35, 1998. doi:10.1016/S0006-8993(98)00642-8.

632. LoParo D, Johansson A, Walum H, Westberg L, Santtila P, Waldman I. Rigorous tests of gene-environment interactions in a lab study of the oxytocin receptor gene (OXTR), alcohol exposure, and aggression. *Am J Med Genet B Neuropsychiatr Genet* 171: 589–602, 2016. doi:10.1002/ajmg.b.32359.

633. LoParo D, Waldman ID. The oxytocin receptor gene (OXTR) is associated with autism spectrum disorder: a meta-analysis. *Mol Psychiatry* 20: 640–646, 2015. doi:10.1038/mp.2014.77.

634. Lopatina O, Liu HX, Amina S, Hashii M, Higashida H. Oxytocin-induced elevation of ADP-ribosyl cyclase activity, cyclic ADP-ribose or Ca(2+) concentrations is involved in autoregulation of oxytocin secretion in the hypothalamus and posterior pituitary in male mice. *Neuropharmacology* 58: 50–55, 2010. doi:10.1016/j.neuropharm.2009.06.012.

635. Loup F, Tribollet E, Dubois-Dauphin M, Dreifuss JJ. Localization of high-affinity binding sites for oxytocin and vasopressin in the human brain. An autoradiographic study. *Brain Res* 555: 220–232, 1991. doi:10.1016/0006-8993(91)90345-V.

636. Lowbridge J, Manning M, Haldar J, Sawyer WH. Synthesis and some pharmacological properties of [4-threonine, 7-glycine]oxytocin, [1-(L-2-hydroxy-3-mercaptopropanoic acid), 4-threonine, 7-glycine]oxytocin (hydroxy[Thr4, Gly7]oxytocin), and [7-Glycine]oxytocin, peptides with high oxytocic-antidiuretic selectivity. *J Med Chem* 20: 120–123, 1977. doi:10.1021/jm00211a025.

637. Lu J, McKinsey TA, Nicol RL, Olson EN. Signal-dependent activation of the MEF2 transcription factor by dissociation from histone deacetylases. *Proc Natl Acad Sci USA* 97: 4070–4075, 2000. doi:10.1073/pnas.080064097.

638. Lucas-Thompson RG, Holman EA. Environmental stress, oxytocin receptor gene (OXTR) polymorphism, and mental health following collective stress. *Horm Behav* 63: 615–624, 2013. doi:10.1016/j.yhbeh.2013.02.015.

639. Ludwig M. Dendritic release of vasopressin and oxytocin. *J Neuroendocrinol* 10: 881–895, 1998. doi:10.1046/j.1365-2826.1998.00279.x.

640. Ludwig M, Apps D, Menzies J, Patel JC, Rice ME. Dendritic release of neurotransmitters. *Compr Physiol* 7: 235–252, 2016. doi:10.1002/cphy.c160007.

641. Ludwig M, Callahan MF, Morris M. Effects of tetrodotoxin on osmotically stimulated central and peripheral vasopressin and oxytocin release. *Neuroendocrinology* 62: 619–627, 1995. doi:10.1159/000127058.

642. Ludwig M, Callahan MF, Neumann I, Landgraf R, Morris M. Systemic osmotic stimulation increases vasopressin and oxytocin release within the supraoptic nucleus. *J Neuroendocrinol* 6: 369–373, 1994. doi:10.1111/j.1365-2826.1994.tb00595.x.

643. Ludwig M, Leng G. Dendritic peptide release and peptide-dependent behaviours. *Nat Rev Neurosci* 7: 126–136, 2006. doi:10.1038/nrn1845.

644. Ludwig M, Sabatier N, Bull PM, Landgraf R, Dayanithi G, Leng G. Intracellular calcium stores regulate activity-dependent neuropeptide release from dendrites. *Nature* 418: 85–89, 2002. doi:10.1038/nature00822.

645. Luhman LA. The effect of intranasal oxytocin on lactation. *Obstet Gynecol* 21: 713–717, 1963.

646. Lukas M, Bredewold R, Neumann ID, Veenema AH. Maternal separation interferes with developmental changes in brain vasopressin and oxytocin receptor binding in male rats. *Neuropharmacology* 58: 78–87, 2010. doi:10.1016/j.neuropharm.2009.06.020.

647. Lukas M, Neumann ID. Social preference and maternal defeat-induced social avoidance in virgin female rats: sex differences in involvement of brain oxytocin and vasopressin. *J Neurosci Methods* 234: 101–107, 2014. doi:10.1016/j.jneumeth.2014.03.013.

648. Lukas M, Toth I, Reber SO, Slattery DA, Veenema AH, Neumann ID. The neuropeptide oxytocin facilitates pro-social behavior and prevents social avoidance in rats and mice. *Neuropsychopharmacology* 36: 2159–2168, 2011. doi:10.1038/npp.2011.95.

649. Lukas M, Toth I, Veenema AH, Neumann ID. Oxytocin mediates rodent social memory within the lateral septum and the medial amygdala depending on the relevance of the social stimulus: male juvenile versus female adult conspecifics. *Psychoneuroendocrinology* 38: 916–926, 2013. doi:10.1016/j.psyneuen.2012.09.018.

650. Ma D, Morris JF. Protein synthetic machinery in the dendrites of the magnocellular neurosecretory neurons of wild-type Long-Evans and homozygous Brattleboro rats. *J Chem Neuroanat* 23: 171–186, 2002. doi:10.1016/S0891-0618(01)00158-2.

651. Mabrouk OS, Kennedy RT. Simultaneous oxytocin and arg-vasopressin measurements in microdialysates using capillary liquid chromatography-mass spectrometry. *J Neurosci Methods* 209: 127–133, 2012. doi:10.1016/j.jneumeth.2012.06.006.

652. MacDonald K, Feifel D. Oxytocin's role in anxiety: a critical appraisal. *Brain Res* 1580: 22–56, 2014. doi:10.1016/j.brainres.2014.01.025.

653. MacLaren DA, Browne RW, Shaw JK, Krishnan Radhakrishnan S, Khare P, España RA, Clark SD. Clozapine N-oxide administration produces behavioral effects in long-evans rats: implications for designing DREADD experiments. *eNeuro* 3: ENEURO.0219–16.2016, 2016. doi:10.1523/ENEURO.0219-16.2016.

654. Madden JR, Clutton-Brock TH. Experimental peripheral administration of oxytocin elevates a suite of cooperative behaviours in a wild social mammal. *Proc Biol Sci* 278: 1189–1194, 2011. doi:10.1098/rspb.2010.1675.

655. Maejima Y, Takahashi S, Takasu K, Takenoshita S, Ueta Y, Shimomura K. Orexin action on oxytocin neurons in the paraventricular nucleus of the hypothalamus. *Neuroreport* 28: 360–366, 2017. doi:10.1097/WNR.0000000000000773.

656. Magalhães ES, Pinto-Mariz F, Bastos-Pinto S, Pontes AT, Prado EA, deAzevedo LC. Immune allergic response in Asperger syndrome. *J Neuroimmunol* 216: 108–112, 2009. doi:10.1016/j.jneuroim.2009.09.015.

657. Mahalati K, Okanoya K, Witt DM, Carter CS. Oxytocin inhibits male sexual behavior in prairie voles. *Pharmacol Biochem Behav* 39: 219–222, 1991. doi:10.1016/0091-3057(91)90426-3.

658. Mahlmann S, Meyerhof W, Hausmann H, Heierhorst J, Schönrock C, Zwiers H, Lederis K, Richter D. Structure, function, and phylogeny of [Arg8]vasotocin receptors from teleost fish and toad. *Proc Natl Acad Sci USA* 91: 1342–1345, 1994. doi:10.1073/pnas.91.4.1342.

659. Mairesse J, Gatta E, Reynaert ML, Marrocco J, Morley-Fletcher S, Soichot M, Deruyter L, Camp GV, Bouwalerh H, Fagioli F, Pittaluga A, Allorge D, Nicoletti F, Maccari S. Activation of presynaptic oxytocin receptors enhances glutamate release in the ventral hippocampus of prenatally restraint stressed rats. *Psychoneuroendocrinology* 62: 36–46, 2015. doi:10.1016/j.psyneuen.2015.07.005.

660. Mak P, Broussard C, Vacy K, Broadbear JH. Modulation of anxiety behavior in the elevated plus maze using peptidic oxytocin and vasopressin receptor ligands in the rat. *J Psychopharmacol* 26: 532–542, 2012. doi:10.1177/0269881111416687.

661. Makani V, Sultana R, Sie KS, Orjiako D, Tatangelo M, Dowling A, Cai J, Pierce W, Allan Butterfield D, Hill J, Park J. Annexin A1 complex mediates oxytocin vesicle transport. *J Neuroendocrinol* 25: 1241–1254, 2013. doi:10.1111/jne.12112.

662. Malik AI, Zai CC, Abu Z, Nowrouzi B, Beitchman JH. The role of oxytocin and oxytocin receptor gene variants in childhood-onset aggression. *Genes Brain Behav* 11: 545–551, 2012. doi:10.1111/j.1601-183X.2012.00776.x.

663. Malik AI, Zai CC, Berall L, Abu Z, Din F, Nowrouzi B, Chen S, Beitchman JH. The role of genetic variants in genes regulating the oxytocin-vasopressin neurohumoral system in childhood-onset aggression. *Psychiatr Genet* 24: 201–210, 2014.

664. Mamrut S, Harony H, Sood R, Shahar-Gold H, Gainer H, Shi YJ, Barki-Harrington L, Wagner S. DNA methylation of specific CpG sites in the promoter region regulates the transcription of the mouse oxytocin receptor. *PLoS One* 8: e56869, 2013. doi:10.1371/journal.pone.0056869.

665. Manbeck KE, Shelley D, Schmidt CE, Harris AC. Effects of oxytocin on nicotine withdrawal in rats. *Pharmacol Biochem Behav* 116: 84–89, 2014. doi:10.1016/j.pbb.2013.11.002.

666. Manning M, Du Vigneaud V. 6-Hemi-D-cystine-oxytocin, a diastereoisomer of the posterior pituitary hormone oxytocin. *J Am Chem Soc* 87: 3978–3982, 1965. doi:10.1021/ja01095a035.

667. Manning M, Kruszynski M, Bankowski K, Olma A, Lammek B, Cheng LL, Klis WA, Seto J, Haldar J, Sawyer WH. Solid-phase synthesis of 16 potent (selective and nonselective) in vivo antagonists of oxytocin. *J Med Chem* 32: 382–391, 1989. doi:10.1021/jm00122a016.

668. Manning M, Sawyer WH. 4-Threonine-oxytocin: a more active and specific oxytocic agent than oxytocin. *Nature* 227: 715–716, 1970. doi:10.1038/227715a0.

669. Manning M, Stoev S, Chini B, Durroux T, Mouillac B, Guillon G. Peptide and non-peptide agonists and antagonists for the vasopressin and oxytocin V1a, V1b, V2 and OT receptors: research tools and potential therapeutic agents. *Prog Brain Res* 170: 473–512, 2008. doi:10.1016/S0079-6123(08)00437-8.

670. Marlin BJ, Mitre M, D'amour JA, Chao MV, Froemke RC. Oxytocin enables maternal behaviour by balancing cortical inhibition. *Nature* 520: 499–504, 2015. doi:10.1038/nature14402.

671. Marsh AA, Yu HH, Pine DS, Blair RJ. Oxytocin improves specific recognition of positive facial expressions. *Psychopharmacology (Berl)* 209: 225–232, 2010. doi:10.1007/s00213-010-1780-4.

672. Martin KC, Barad M, Kandel ER. Local protein synthesis and its role in synapse-specific plasticity. *Curr Opin Neurobiol* 10: 587–592, 2000. doi:10.1016/S0959-4388(00)00128-8.

673. Martin R, Geis R, Holl R, Schäfer M, Voigt KH. Co-existence of unrelated peptides in oxytocin and vasopressin terminals of rat neurohypophyses: immunoreactive methionine-enkephalin-, leucine-enkephalin- and cholecystokinin-like substances. *Neuroscience* 8: 213–227, 1983. doi:10.1016/0306-4522(83)90061-1.

674. Mascolo A, Sessa M, Scavone C, De Angelis A, Vitale C, Berrino L, Rossi F, Rosano G, Capuano A. New and old roles of the peripheral and brain renin-angiotensin-aldosterone system (RAAS): Focus on cardiovascular and neurological diseases. *Int J Cardiol* 227: 734–742, 2017. doi:10.1016/j.ijcard.2016.10.069.

675. McCann MJ, Rogers RC. Oxytocin excites gastric-related neurones in rat dorsal vagal complex. *J Physiol* 428: 95–108, 1990. doi:10.1113/jphysiol.1990.sp018202.

676. McCann MJ, Verbalis JG, Stricker EM. Capsaicin pretreatment attenuates multiple responses to cholecystokinin in rats. *J Auton Nerv Syst* 23: 265–272, 1988. doi:10.1016/0165-1838(88)90101-4.

677. McCarthy MM, Curran GH, Feder HH. Excitatory amino acid modulation of lordosis in the rat. *Neurosci Lett* 126: 94–97, 1991. doi:10.1016/0304-3940(91)90380-C.

678. McCarthy MM, Kaufman LC, Brooks PJ, Pfaff DW, Schwartz-Giblin S. Estrogen modulation of mRNA levels for the two forms of glutamic acid decarboxylase (GAD) in female rat brain. *J Comp Neurol* 360: 685–697, 1995. doi:10.1002/cne.903600412.

679. McCarthy MM, Kleopoulos SP, Mobbs CV, Pfaff DW. Infusion of antisense oligodeoxynucleotides to the oxytocin receptor in the ventromedial hypothalamus reduces estrogen-induced sexual receptivity and oxytocin receptor binding in the female rat. *Neuroendocrinology* 59: 432–440, 1994. doi:10.1159/000126689.

680. McCullough ME, Churchland PS, Mendez AJ. Problems with measuring peripheral oxytocin: can the data on oxytocin and human behavior be trusted? *Neurosci Biobehav Rev* 37: 1485–1492, 2013. doi:10.1016/j.neubiorev.2013.04.018.

681. McGregor IS, Bowen MT. Breaking the loop: oxytocin as a potential treatment for drug addiction. *Horm Behav* 61: 331–339, 2012. doi:10.1016/j.yhbeh.2011.12.001.

682. McGregor IS, Callaghan PD, Hunt GE. From ultrasocial to antisocial: a role for oxytocin in the acute reinforcing effects and long-term adverse consequences of drug use? *Br J Pharmacol* 154: 358–368, 2008. doi:10.1038/bjp.2008.132.

683. McNeilly AS, Robinson IC, Houston MJ, Howie PW. Release of oxytocin and prolactin in response to suckling. *Br Med J (Clin Res Ed)* 286: 257–259, 1983. doi:10.1136/bmj.286.6361.257.

684. McRae-Clark AL, Baker NL, Maria MM, Brady KT. Effect of oxytocin on craving and stress response in marijuana-dependent individuals: a pilot study. *Psychopharmacology (Berl)* 228: 623–631, 2013. doi:10.1007/s00213-013-3062-4.

685. Meddle SL, Bishop VR, Gkoumassi E, van Leeuwen FW, Douglas AJ. Dynamic changes in oxytocin receptor expression and activation at parturition in the rat brain. *Endocrinology* 148: 5095–5104, 2007. doi:10.1210/en.2007-0615.

686. Meinlschmidt G, Martin C, Neumann ID, Heinrichs M. Maternal cortisol in late pregnancy and hypothalamic-pituitary-adrenal reactivity to psychosocial stress postpartum in women. *Stress* 13: 163–171, 2010. doi:10.3109/10253890903128632.

687. Melin P, Kihlstroem JE. Influence of oxytocin on sexual behavior in male rabbits. *Endocrinology* 73: 433–435, 1963. doi:10.1210/endo-73-4-433.

688. Melis MR, Melis T, Cocco C, Succu S, Sanna F, Pillolla G, Boi A, Ferri GL, Argiolas A. Oxytocin injected into the ventral tegmental area induces penile erection and increases extracellular dopamine in the nucleus accumbens and paraventricular nucleus of the hypothalamus of male rats. *Eur J Neurosci* 26: 1026–1035, 2007. doi:10.1111/j.1460-9568.2007.05721.x.

689. Melis MR, Spano MS, Succu S, Argiolas A. The oxytocin antagonist d(CH2)5Tyr(Me)2-Orn8-vasotocin reduces non-contact penile erections in male rats. *Neurosci Lett* 265: 171–174, 1999. doi:10.1016/S0304-3940(99)00236-0.

690. Melis MR, Succu S, Sanna F, Boi A, Argiolas A. Oxytocin injected into the ventral subiculum or the posteromedial cortical nucleus of the amygdala induces penile erection and increases extracellular dopamine levels in the nucleus accumbens of male rats. *Eur J Neurosci* 30: 1349–1357, 2009. doi:10.1111/j.1460-9568.2009.06912.x.

691. Menaouar A, Florian M, Wang D, Danalache B, Jankowski M, Gutkowska J. Antihypertrophic effects of oxytocin in rat ventricular myocytes. *Int J Cardiol* 175: 38–49, 2014. doi:10.1016/j.ijcard.2014.04.174.

692. Mendez JA, Bourque MJ, Fasano C, Kortleven C, Trudeau LE. Somatodendritic dopamine release requires synaptotagmin 4 and 7 and the participation of voltage-gated calcium channels. *J Biol Chem* 286: 23928–23937, 2011. doi:10.1074/jbc.M111.218032.

692a. Menon R, Grund T, Zoicas I, Althammer F, Fiedler D, Biermeier V, Bosch OJ, Hiraoka Y, Nishimori K, Nishimori K, Eliava M, et al. Oxytocin signaling in the lateral septum prevents social fear during lactation. *Curr Biol* 28: 1066–1078, 2018.

693. Mens WB, Witter A, van Wimersma Greidanus TB. Penetration of neurohypophyseal hormones from plasma into cerebrospinal fluid (CSF): half-times of disappearance of these neuropeptides from CSF. *Brain Res* 262: 143–149, 1983. doi:10.1016/0006-8993(83)90478-X.

694. Meyer-Lindenberg A, Domes G, Kirsch P, Heinrichs M. Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine. *Nat Rev Neurosci* 12: 524–538, 2011. doi:10.1038/nrn3044.

695. Meyer-Lindenberg A, Tost H. Neural mechanisms of social risk for psychiatric disorders. *Nat Neurosci* 15: 663–668, 2012. doi:10.1038/nn.3083.

696. Meynen G, Unmehopa UA, Hofman MA, Swaab DF, Hoogendijk WJ. Hypothalamic oxytocin mRNA expression and melancholic depression. *Mol Psychiatry* 12: 118–119, 2007. doi:10.1038/sj.mp.4001911.

697. Michalak A, Biala G. Calcium homeostasis and protein kinase/phosphatase balance participate in nicotine-induced memory improvement in passive avoidance task in mice. *Behav Brain Res* 317: 27–36, 2017. doi:10.1016/j.bbr.2016.09.023.

698. Michaud JL, Boucher F, Melnyk A, Gauthier F, Goshu E, Lévy E, Mitchell GA, Himms-Hagen J, Fan CM. Sim1 haploinsufficiency causes hyperphagia, obesity and reduction of the paraventricular nucleus of the hypothalamus. *Hum Mol Genet* 10: 1465–1473, 2001. doi:10.1093/hmg/10.14.1465.

699. Michaud JL, Rosenquist T, May NR, Fan CM. Development of neuroendocrine lineages requires the bHLH-PAS transcription factor SIM1. *Genes Dev* 12: 3264–3275, 1998. doi:10.1101/gad.12.20.3264.

700. Miedlar JA, Rinaman L, Vollmer RR, Amico JA. Oxytocin gene deletion mice overconsume palatable sucrose solution but not palatable lipid emulsions. *Am J Physiol Regul Integr Comp Physiol* 293: R1063–R1068, 2007. doi:10.1152/ajpregu.00228.2007.

701. Mitchell JM, Arcuni PA, Weinstein D, Woolley JD. Intranasal oxytocin selectively modulates social perception, craving, and approach behavior in subjects with alcohol use disorder. *J Addict Med* 10: 182–189, 2016. doi:10.1097/ADM.0000000000000213.

702. Mitre M, Marlin BJ, Schiavo JK, Morina E, Norden SE, Hackett TA, Aoki CJ, Chao MV, Froemke RC. A distributed network for social cognition enriched for oxytocin receptors. *J Neurosci* 36: 2517–2535, 2016. doi:10.1523/JNEUROSCI.2409-15.2016.

703. Mittaud P, Labourdette G, Zingg H, Guenot-Di Scala D. Neurons modulate oxytocin receptor expression in rat cultured astrocytes: involvement of TGF-beta and membrane components. *Glia* 37: 169–177, 2002. doi:10.1002/glia.10029.

704. Modi ME, Connor-Stroud F, Landgraf R, Young LJ, Parr LA. Aerosolized oxytocin increases cerebrospinal fluid oxytocin in rhesus macaques. *Psychoneuroendocrinology* 45: 49–57, 2014. doi:10.1016/j.psyneuen.2014.02.011.

705. Modi ME, Inoue K, Barrett CE, Kittelberger KA, Smith DG, Landgraf R, Young LJ. Melanocortin receptor agonists facilitate oxytocin-dependent partner preference formation in the prairie vole. *Neuropsychopharmacology* 40: 1856–1865, 2015. doi:10.1038/npp.2015.35.

706. Mody N, Leitch J, Armstrong C, Dixon J, Cohen P. Effects of MAP kinase cascade inhibitors on the MKK5/ERK5 pathway. *FEBS Lett* 502: 21–24, 2001. doi:10.1016/S0014-5793(01)02651-5.

707. Mohr E, Bahnsen U, Kiessling C, Richter D. Expression of the vasopressin and oxytocin genes in rats occurs in mutually exclusive sets of hypothalamic neurons. *FEBS Lett* 242: 144–148, 1988. doi:10.1016/0014-5793(88)81003-2.

708. Mohr E, Fehr S, Richter D. Axonal transport of neuropeptide encoding mRNAs within the hypothalamo-hypophyseal tract of rats. *EMBO J* 10: 2419–2424, 1991.

709. Mohr E, Hillers M, Ivell R, Haulica ID, Richter D. Expression of the vasopressin and oxytocin genes in human hypothalami. *FEBS Lett* 193: 12–16, 1985. doi:10.1016/0014-5793(85)80069-7.

710. Mohr E, Morris JF, Richter D. Differential subcellular mRNA targeting: deletion of a single nucleotide prevents the transport to axons but not to dendrites of rat hypothalamic magnocellular neurons. *Proc Natl Acad Sci USA* 92: 4377–4381, 1995. doi:10.1073/pnas.92.10.4377.

711. Mohr E, Richter D. Local synthesis of the rat Vasopressin precursor in dendrites of in vitro cultured nerve cells. *Brain Res Mol Brain Res* 114: 115–122, 2003. doi:10.1016/S0169-328X(03)00137-2.

712. Monteleone AM, Scognamiglio P, Volpe U, Di Maso V, Monteleone P. Investigation of oxytocin secretion in anorexia nervosa and bulimia nervosa: relationships to temperament personality dimensions. *Eur Eat Disord Rev* 24: 52–56, 2016. doi:10.1002/erv.2391.

713. Moody KM, Steinman JL, Komisaruk BR, Adler NT. Pelvic neurectomy blocks oxytocin-facilitated sexual receptivity in rats. *Physiol Behav* 56: 1057–1060, 1994. doi:10.1016/0031-9384(94)90343-3.

714. Moos F, Freund-Mercier MJ, Guerné Y, Guerné JM, Stoeckel ME, Richard P. Release of oxytocin and vasopressin by magnocellular nuclei in vitro: specific facilitatory

effect of oxytocin on its own release. *J Endocrinol* 102: 63–72, 1984. doi:10.1677/joe.0.1020063.

715. Moos F, Gouzènes L, Brown D, Dayanithi G, Sabatier N, Boissin L, Rabié A, Richard P. New aspects of firing pattern autocontrol in oxytocin and vasopressin neurones. *Adv Exp Med Biol* 449: 153–162, 1998. doi:10.1007/978-1-4615-4871-3_18.

716. Moos F, Ingram CD, Wakerley JB, Guerné Y, Freund-Mercier MJ, Richard P. Oxytocin in the bed nucleus of the stria terminalis and lateral septum facilitates bursting of hypothalamic oxytocin neurons in suckled rats. *J Neuroendocrinol* 3: 163–171, 1991. doi:10.1111/j.1365-2826.1991.tb00259.x.

717. Moos F, Poulain DA, Rodriguez F, Guerné Y, Vincent JD, Richard P. Release of oxytocin within the supraoptic nucleus during the milk ejection reflex in rats. *Exp Brain Res* 76: 593–602, 1989. doi:10.1007/BF00248916.

718. Moos F, Richard P. Paraventricular and supraoptic bursting oxytocin cells in rat are locally regulated by oxytocin and functionally related. *J Physiol* 408: 1–18, 1989. doi:10.1113/jphysiol.1989.sp017442.

719. Mor M, Nardone S, Sams DS, Elliott E. Hypomethylation of miR-142 promoter and upregulation of microRNAs that target the oxytocin receptor gene in the autism prefrontal cortex. *Mol Autism* 6: 46, 2015. doi:10.1186/s13229-015-0040-1.

720. Moraitis AA, Cordeaux Y, Charnock-Jones DS, Smith GC. The effect of an oxytocin receptor antagonist (Retosiban, GSK221149A) on the response of human myometrial explants to prolonged mechanical stretch. *Endocrinology* 156: 3511–3516, 2015. doi:10.1210/en.2015-1378.

721. Morales-Rivera A, Hernández-Burgos MM, Martínez-Rivera A, Pérez-Colón J, Rivera R, Montalvo J, Rodríguez-Borrero E, Maldonado-Vlaar CS. Anxiolytic effects of oxytocin in cue-induced cocaine seeking behavior in rats. *Psychopharmacology (Berl)* 231: 4145–4155, 2014. doi:10.1007/s00213-014-3553-y.

722. Moreno-López Y, Martínez-Lorenzana G, Condés-Lara M, Rojas-Piloni G. Identification of oxytocin receptor in the dorsal horn and nociceptive dorsal root ganglion neurons. *Neuropeptides* 47: 117–123, 2013. doi:10.1016/j.npep.2012.09.008.

723. Morris JF, Pow DV. Widespread release of peptides in the central nervous system: quantitation of tannic acid-captured exocytoses. *Anat Rec* 231: 437–445, 1991. doi:10.1002/ar.1092310406.

724. Morrow EM, Yoo SY, Flavell SW, Kim TK, Lin Y, Hill RS, Mukaddes NM, Balkhy S, Gascon G, Hashmi A, Al-Saad S, Ware J, Joseph RM, Greenblatt R, Gleason D, Ertelt JA, Apse KA, Bodell A, Partlow JN, Barry B, Yao H, Markianos K, Ferland RJ, Greenberg ME, Walsh CA. Identifying autism loci and genes by tracing recent shared ancestry. *Science* 321: 218–223, 2008. doi:10.1126/science.1157657.

725. Mountjoy KG, Mortrud MT, Low MJ, Simerly RB, Cone RD. Localization of the melanocortin-4 receptor (MC4-R) in neuroendocrine and autonomic control circuits in the brain. *Mol Endocrinol* 8: 1298–1308, 1994.

726. Murgatroyd C, Wigger A, Frank E, Singewald N, Bunck M, Holsboer F, Landgraf R, Spengler D. Impaired repression at a vasopressin promoter polymorphism underlies overexpression of vasopressin in a rat model of trait anxiety. *J Neurosci* 24: 7762–7770, 2004. doi:10.1523/JNEUROSCI.1614-04.2004.

727. Murphy MR, Checkley SA, Seckl JR, Lightman SL. Naloxone inhibits oxytocin release at orgasm in man. *J Clin Endocrinol Metab* 71: 1056–1058, 1990. doi:10.1210/jcem-71-4-1056.

728. Murphy MR, Seckl JR, Burton S, Checkley SA, Lightman SL. Changes in oxytocin and vasopressin secretion during sexual activity in men. *J Clin Endocrinol Metab* 65: 738–741, 1987. doi:10.1210/jcem-65-4-738.

729. Murtazina DA, Chung D, Ulloa A, Bryan E, Galan HL, Sanborn BM. TRPC1, STIM1, and ORAI influence signal-regulated intracellular and endoplasmic reticulum calcium dynamics in human myometrial cells. *Biol Reprod* 85: 315–326, 2011. doi:10.1095/biolreprod.111.091082.

730. Muscatelli F, Abrous DN, Massacrier A, Boccaccio I, Le Moal M, Cau P, Cremer H. Disruption of the mouse Necdin gene results in hypothalamic and behavioral alterations reminiscent of the human Prader-Willi syndrome. *Hum Mol Genet* 9: 3101–3110, 2000. doi:10.1093/hmg/9.20.3101.

731. Muthaiah VPK, Michael FM, Palaniappan T, Rajan SS, Chandrasekar K, Venkatachalam S. JNK1 and JNK3 play a significant role in both neuronal apoptosis and necrosis. Evaluation based on in vitro approach using tert-butylhydroperoxide induced oxidative stress in neuro-2A cells and perturbation through 3-aminobenzamide. *Toxicol In Vitro* 41: 168–178, 2017. doi:10.1016/j.tiv.2017.02.015.

732. Myers AJ, Williams L, Gatt JM, McAuley-Clark EZ, Dobson-Stone C, Schofield PR, Nemeroff CB. Variation in the oxytocin receptor gene is associated with increased risk for anxiety, stress and depression in individuals with a history of exposure to early life stress. *J Psychiatr Res* 59: 93–100, 2014. doi:10.1016/j.jpsychires.2014.08.021.

733. Nagasawa M, Kikusui T, Onaka T, Ohta M. Dog's gaze at its owner increases owner's urinary oxytocin during social interaction. *Horm Behav* 55: 434–441, 2009. doi:10.1016/j.yhbeh.2008.12.002.

734. Nagasawa M, Mitsui S, En S, Ohtani N, Ohta M, Sakuma Y, Onaka T, Mogi K, Kikusui T. Social evolution. Oxytocin-gaze positive loop and the coevolution of human-dog bonds. *Science* 348: 333–336, 2015. doi:10.1126/science.1261022.

735. Nakahara M, Shimozawa M, Nakamura Y, Irino Y, Morita M, Kudo Y, Fukami K. A novel phospholipase C, PLC(eta)2, is a neuron-specific isozyme. *J Biol Chem* 280: 29128–29134, 2005. doi:10.1074/jbc.M503817200.

736. Nakajima M, Görlich A, Heintz N. Oxytocin modulates female sociosexual behavior through a specific class of prefrontal cortical interneurons. *Cell* 159: 295–305, 2014. doi:10.1016/j.cell.2014.09.020.

737. Naylor AM, Pittman QJ, Veale WL. Stimulation of vasopressin release in the ventral septum of the rat brain suppresses prostaglandin E1 fever. *J Physiol* 399: 177–189, 1988. doi:10.1113/jphysiol.1988.sp017074.

738. Ne'eman R, Perach-Barzilay N, Fischer-Shofty M, Atias A, Shamay-Tsoory SG. Intranasal administration of oxytocin increases human aggressive behavior. *Horm Behav* 80: 125–131, 2016. doi:10.1016/j.yhbeh.2016.01.015.

739. Neumann I, Douglas AJ, Pittman QJ, Russell JA, Landgraf R. Oxytocin released within the supraoptic nucleus of the rat brain by positive feedback action is involved in parturition-related events. *J Neuroendocrinol* 8: 227–233, 1996. doi:10.1046/j.1365-2826.1996.04557.x.

740. Neumann I, Koehler E, Landgraf R, Summy-Long J. An oxytocin receptor antagonist infused into the supraoptic nucleus attenuates intranuclear and peripheral release of oxytocin during suckling in conscious rats. *Endocrinology* 134: 141–148, 1994. doi:10.1210/endo.134.1.8275928.

741. Neumann I, Landgraf R. Septal and hippocampal release of oxytocin, but not vasopressin, in the conscious lactating rat during suckling. *J Neuroendocrinol* 1: 305–308, 1989. doi:10.1111/j.1365-2826.1989.tb00120.x.

742. Neumann I, Landgraf R, Takahashi Y, Pittman QJ, Russell JA. Stimulation of oxytocin release within the supraoptic nucleus and into blood by CCK-8. *Am J Physiol Regul Integr Comp Physiol* 267: R1626–R1631, 1994.

743. Neumann I, Ludwig M, Engelmann M, Pittman QJ, Landgraf R. Simultaneous microdialysis in blood and brain: oxytocin and vasopressin release in response to central and peripheral osmotic stimulation and suckling in the rat. *Neuroendocrinology* 58: 637–645, 1993. doi:10.1159/000126604.

744. Neumann I, Russell JA, Landgraf R. Oxytocin and vasopressin release within the supraoptic and paraventricular nuclei of pregnant, parturient and lactating rats: a microdialysis study. *Neuroscience* 53: 65–75, 1993. doi:10.1016/0306-4522(93)90285-N.

745. Neumann I, Schwarzberg H, Landgraf R. Measurement of septal release of vasopressin and oxytocin by the push-pull technique following electrical stimulation of the paraventricular nucleus of rats. *Brain Res* 462: 181–184, 1988. doi:10.1016/0006-8993(88)90603-8.

746. Neumann ID. The advantage of social living: brain neuropeptides mediate the beneficial consequences of sex and motherhood. *Front Neuroendocrinol* 30: 483–496, 2009. doi:10.1016/j.yfrne.2009.04.012.

747. Neumann ID. Alterations in behavioral and neuroendocrine stress coping strategies in pregnant, parturient and lactating rats. *Prog Brain Res* 133: 143–152, 2001. doi:10.1016/S0079-6123(01)33011-X.

748. Neumann ID. Brain mechanisms underlying emotional alterations in the peripartum period in rats. *Depress Anxiety* 17: 111–121, 2003. doi:10.1002/da.10070.

749. Neumann ID. Oxytocin: the neuropeptide of love reveals some of its secrets. *Cell Metab* 5: 231–233, 2007. doi:10.1016/j.cmet.2007.03.008.

750. Neumann ID. Stimuli and consequences of dendritic release of oxytocin within the brain. *Biochem Soc Trans* 35: 1252–1257, 2007. doi:10.1042/BST0351252.

751. Neumann ID, Johnstone HA, Hatzinger M, Liebsch G, Shipston M, Russell JA, Landgraf R, Douglas AJ. Attenuated neuroendocrine responses to emotional and physical stressors in pregnant rats involve adenohypophysial changes. *J Physiol* 508: 289–300, 1998. doi:10.1111/j.1469-7793.1998.289br.x.

752. Neumann ID, Krömer SA, Toschi N, Ebner K. Brain oxytocin inhibits the (re)activity of the hypothalamo-pituitary-adrenal axis in male rats: involvement of hypothalamic and limbic brain regions. *Regul Pept* 96: 31–38, 2000. doi:10.1016/S0167-0115(00)00197-X.

753. Neumann ID, Landgraf R. Balance of brain oxytocin and vasopressin: implications for anxiety, depression, and social behaviors. *Trends Neurosci* 35: 649–659, 2012. doi:10.1016/j.tins.2012.08.004.

754. Neumann ID, Maloumby R, Beiderbeck DI, Lukas M, Landgraf R. Increased brain and plasma oxytocin after nasal and peripheral administration in rats and mice. *Psychoneuroendocrinology* 38: 1985–1993, 2013. doi:10.1016/j.psyneuen.2013.03.003.

755. Neumann ID, Slattery DA. Oxytocin in general anxiety and social fear: a translational approach. *Biol Psychiatry* 79: 213–221, 2016. doi:10.1016/j.biopsych.2015.06.004.

756. Neumann ID, Torner L, Toschi N, Veenema AH. Oxytocin actions within the supraoptic and paraventricular nuclei: differential effects on peripheral and intranuclear vasopressin release. *Am J Physiol Regul Integr Comp Physiol* 291: R29–R36, 2006. doi:10.1152/ajpregu.00763.2005.

757. Neumann ID, Torner L, Wigger A. Brain oxytocin: differential inhibition of neuroendocrine stress responses and anxiety-related behaviour in virgin, pregnant and lactating rats. *Neuroscience* 95: 567–575, 2000. doi:10.1016/S0306-4522(99)00433-9.

758. Neumann ID, Toschi N, Ohl F, Torner L, Krömer SA. Maternal defence as an emotional stressor in female rats: correlation of neuroendocrine and behavioural parameters and involvement of brain oxytocin. *Eur J Neurosci* 13: 1016–1024, 2001. doi:10.1046/j.0953-816x.2001.01460.x.

759. Neumann ID, Veenema AH, Beiderbeck DI. Aggression and anxiety: social context and neurobiological links. *Front Behav Neurosci* 4: 12, 2010. doi:10.3389/fnbeh.2010.00012.

760. Neumann ID, Wigger A, Liebsch G, Holsboer F, Landgraf R. Increased basal activity of the hypothalamo-pituitary-adrenal axis during pregnancy in rats bred for high anxiety-related behaviour. *Psychoneuroendocrinology* 23: 449–463, 1998. doi:10.1016/S0306-4530(98)00023-7.

761. Neumann ID, Wigger A, Torner L, Holsboer F, Landgraf R. Brain oxytocin inhibits basal and stress-induced activity of the hypothalamo-pituitary-adrenal axis in male and female rats: partial action within the paraventricular nucleus. *J Neuroendocrinol* 12: 235–243, 2000. doi:10.1046/j.1365-2826.2000.00442.x.

762. Nillni EA. Regulation of the hypothalamic thyrotropin releasing hormone (TRH) neuron by neuronal and peripheral inputs. *Front Neuroendocrinol* 31: 134–156, 2010. doi:10.1016/j.yfrne.2010.01.001.

763. Ninan I. Oxytocin suppresses basal glutamatergic transmission but facilitates activity-dependent synaptic potentiation in the medial prefrontal cortex. *J Neurochem* 119: 324–331, 2011. doi:10.1111/j.1471-4159.2011.07430.x.

764. Nishimori K, Young LJ, Guo Q, Wang Z, Insel TR, Matzuk MM. Oxytocin is required for nursing but is not essential for parturition or reproductive behavior. *Proc Natl Acad Sci USA* 93: 11699–11704, 1996. doi:10.1073/pnas.93.21.11699.

765. Nishioka T, Anselmo-Franci JA, Li P, Callahan MF, Morris M. Stress increases oxytocin release within the hypothalamic paraventricular nucleus. *Brain Res* 781: 57–61, 1998. doi:10.1016/S0006-8993(97)01159-1.

766. Nishitani S, Moriya T, Kondo Y, Sakuma Y, Shinohara K. Induction of Fos immunoreactivity in oxytocin neurons in the paraventricular nucleus after female odor exposure in male rats: effects of sexual experience. *Cell Mol Neurobiol* 24: 283–291, 2004. doi:10.1023/B:CEMN.0000018622.44317.14.

767. Nohara A, Ohmichi M, Koike K, Masumoto N, Kobayashi M, Akahane M, Ikegami H, Hirota K, Miyake A, Murata Y. The role of mitogen-activated protein kinase in oxytocin-induced contraction of uterine smooth muscle in pregnant rat. *Biochem Biophys Res Commun* 229: 938–944, 1996. doi:10.1006/bbrc.1996.1905.

768. Nomura M, Saito J, Ueta Y, Muglia LJ, Pfaff DW, Ogawa S. Enhanced up-regulation of corticotropin-releasing hormone gene expression in response to restraint stress in the hypothalamic paraventricular nucleus of oxytocin gene-deficient male mice. *J Neuroendocrinol* 15: 1054–1061, 2003. doi:10.1046/j.1365-2826.2003.01095.x.

769. Norbury R, Mackay CE, Cowen PJ, Goodwin GM, Harmer CJ. Short-term antidepressant treatment and facial processing. Functional magnetic resonance imaging study. *Br J Psychiatry* 190: 531–532, 2007. doi:10.1192/bjp.bp.106.031393.

770. Normandin JJ, Murphy AZ. Somatic genital reflexes in rats with a nod to humans: anatomy, physiology, and the role of the social neuropeptides. *Horm Behav* 59: 656–665, 2011. doi:10.1016/j.yhbeh.2011.02.006.

771. Nowakowska E, Kus K, Bobkiewicz-Kozłowska T, Hertmanowska H. Role of neuropeptides in antidepressant and memory improving effects of venlafaxine. *Pol J Pharmacol* 54: 605–613, 2002.

772. Numan M, Young LJ. Neural mechanisms of mother-infant bonding and pair bonding: Similarities, differences, and broader implications. *Horm Behav* 77: 98–112, 2016. doi:10.1016/j.yhbeh.2015.05.015.

773. Nyuyki KD, Waldherr M, Baeuml S, Neumann ID. Yes, I am ready now: differential effects of paced versus unpaced mating on anxiety and central oxytocin release in female rats. *PLoS One* 6: e23599, 2011. doi:10.1371/journal.pone.0023599.

774. O'Donohue TL, Jacobowitz DM. Studies of alpha-MSH-containing nerves in the brain. *Prog Biochem Pharmacol* 16: 69–83, 1980.

775. O'Shea RD, Gundlach AL. Regulation of cholecystokinin receptors in the hypothalamus of the rat: reciprocal changes in magnocellular nuclei induced by food deprivation and dehydration. *J Neuroendocrinol* 5: 697–704, 1993. doi:10.1111/j.1365-2826.1993.tb00542.x.

776. Ocskó T, Gálfi M, Radács M, Molnár Z, Kis GK, Rákosi K, Molnár AH, László F, László FA, Varga C. Effects of orexin-monoaminergic interactions on oxytocin secretion in rat neurohypophyseal cell cultures. *Regul Pept* 175: 43–48, 2012. doi:10.1016/j.regpep.2012.01.002.

777. Oettl LL, Ravi N, Schneider M, Scheller MF, Schneider P, Mitre M, da Silva Gouveia M, Froemke RC, Chao MV, Young WS, Meyer-Lindenberg A, Grinevich V, Shusterman R, Kelsch W. Oxytocin enhances social recognition by modulating cortical control of early olfactory processing. *Neuron* 90: 609–621, 2016. doi:10.1016/j.neuron.2016.03.033.

778. Ogawa S, Kudo S, Kitsunai Y, Fukuchi S. Increase in oxytocin secretion at ejaculation in male. *Clin Endocrinol (Oxf)* 13: 95–97, 1980. doi:10.1111/j.1365-2265.1980.tb01027.x.

779. Ogawa T, Mikuni M, Kuroda Y, Muneoka K, Mori KJ, Takahashi K. Periodic maternal deprivation alters stress response in adult offspring: potentiates the negative feedback regulation of restraint stress-induced adrenocortical response and reduces the frequencies of open field-induced behaviors. *Pharmacol Biochem Behav* 49: 961–967, 1994. doi:10.1016/0091-3057(94)90250-X.

780. Ohkoshi N, Komatsu Y, Mizusawa H, Kanazawa I. Primary position upbeat nystagmus increased on downward gaze: clinicopathologic study of a patient with multiple sclerosis. *Neurology* 50: 551–553, 1998. doi:10.1212/WNL.50.2.551.

781. Okimoto N, Bosch OJ, Slattery DA, Pflaum K, Matsushita H, Wei FY, Ohmori M, Nishiki T, Ohmori I, Hiramatsu Y, Matsui H, Neumann ID, Tomizawa K. RGS2 mediates the anxiolytic effect of oxytocin. *Brain Res* 1453: 26–33, 2012. doi:10.1016/j.brainres.2012.03.012.

782. Olazábal DE, Young LJ. Species and individual differences in juvenile female alloparental care are associated with oxytocin receptor density in the striatum and the lateral septum. *Horm Behav* 49: 681–687, 2006. doi:10.1016/j.yhbeh.2005.12.010.

783. Olson BR, Drutarosky MD, Chow MS, Hruby VJ, Stricker EM, Verbalis JG. Oxytocin and an oxytocin agonist administered centrally decrease food intake in rats. *Peptides* 12: 113–118, 1991. doi:10.1016/0196-9781(91)90176-P.

784. Olson BR, Hoffman GE, Sved AF, Stricker EM, Verbalis JG. Cholecystokinin induces c-fos expression in hypothalamic oxytocinergic neurons projecting to the dorsal vagal complex. *Brain Res* 569: 238–248, 1992. doi:10.1016/0006-8993(92)90635-M.

785. Onaka T, Yagi K. Effects of novelty stress on vasopressin and oxytocin secretion by the pituitary in the rat. *J Neuroendocrinol* 5: 365–369, 1993. doi:10.1111/j.1365-2826.1993.tb00496.x.

786. Ondrejcakova M, Barancik M, Bartekova M, Ravingerova T, Jezova D. Prolonged oxytocin treatment in rats affects intracellular signaling and induces myocardial protection against infarction. *Gen Physiol Biophys* 31: 261–270, 2012. doi:10.4149/gpb_2012_030.

787. Ophir AG, Gessel A, Zheng DJ, Phelps SM. Oxytocin receptor density is associated with male mating tactics and social monogamy. *Horm Behav* 61: 445–453, 2012. doi:10.1016/j.yhbeh.2012.01.007.

788. Orsini CA, Maren S. Neural and cellular mechanisms of fear and extinction memory formation. *Neurosci Biobehav Rev* 36: 1773–1802, 2012. doi:10.1016/j.neubiorev.2011.12.014.

789. Ostrowski NL. Oxytocin receptor mRNA expression in rat brain: implications for behavioral integration and reproductive success. *Psychoneuroendocrinology* 23: 989–1004, 1998. doi:10.1016/S0306-4530(98)00070-5.

790. Ostrowski NL, Young WS III, Lolait SJ. Estrogen increases renal oxytocin receptor gene expression. *Endocrinology* 136: 1801–1804, 1995. doi:10.1210/endo.136.4.7895693.

791. Ott I, Scott JC. The action of glandular extracts upon the contractions of the uterus. *J Exp Med* 11: 326–330, 1909. doi:10.1084/jem.11.2.326.

792. Ovsepian SV, Dolly JO. Dendritic SNAREs add a new twist to the old neuron theory. *Proc Natl Acad Sci USA* 108: 19113–19120, 2011. doi:10.1073/pnas.1017235108.

793. Owen SF, Tuncdemir SN, Bader PL, Tirko NN, Fishell G, Tsien RW. Oxytocin enhances hippocampal spike transmission by modulating fast-spiking interneurons. *Nature* 500: 458–462, 2013. doi:10.1038/nature12330.

794. Ozsoy S, Esel E, Kula M. Serum oxytocin levels in patients with depression and the effects of gender and antidepressant treatment. *Psychiatry Res* 169: 249–252, 2009. doi:10.1016/j.psychres.2008.06.034.

795. Pagani JH, Williams Avram SK, Cui Z, Song J, Mezey É, Senerth JM, Baumann MH, Young WS. Raphe serotonin neuron-specific oxytocin receptor knockout reduces aggression without affecting anxiety-like behavior in male mice only. *Genes Brain Behav* 14: 167–176, 2015. doi:10.1111/gbb.12202.

796. Palmer CW, Amundson SD, Brito LF, Waldner CL, Barth AD. Use of oxytocin and cloprostenol to facilitate semen collection by electroejaculation or transrectal massage in bulls. *Anim Reprod Sci* 80: 213–223, 2004. doi:10.1016/j.anireprosci.2003.07.003.

797. Palus K, Chrobok L, Lewandowski MH. Orexins/hypocretins modulate the activity of NPY-positive and -negative neurons in the rat intergeniculate leaflet via OX1 and OX2 receptors. *Neuroscience* 300: 370–380, 2015. doi:10.1016/j.neuroscience.2015.05.039.

798. Pantazatos SP, Huang YY, Rosoklija GB, Dwork AJ, Arango V, Mann JJ. Whole-transcriptome brain expression and exon-usage profiling in major depression and suicide: evidence for altered glial, endothelial and ATPase activity. *Mol Psychiatry* 22: 760–773, 2017. doi:10.1038/mp.2016.130.

799. Paré P, Paixão-Côrtes VR, Tovo-Rodrigues L, Vargas-Pinilla P, Viscardi LH, Salzano FM, Henkes LE, Bortolini MC. Oxytocin and arginine vasopressin receptor evolution: implications for adaptive novelties in placental mammals. *Genet Mol Biol* 39: 646–657, 2016. doi:10.1590/1678-4685-gmb-2015-0323.

800. Parfitt DB, Levin JK, Saltstein KP, Klayman AS, Greer LM, Helmreich DL. Differential early rearing environments can accentuate or attenuate the responses to stress in male C57BL/6 mice. *Brain Res* 1016: 111–118, 2004. doi:10.1016/j.brainres.2004.04.077.

801. Park ES, Echetebu CO, Soloff S, Soloff MS. Oxytocin stimulation of RGS2 mRNA expression in cultured human myometrial cells. *Am J Physiol Endocrinol Metab* 282: E580–E584, 2002. doi:10.1152/ajpendo.00437.2001.

802. Parker KJ, Garner JP, Libove RA, Hyde SA, Hornbeak KB, Carson DS, Liao CP, Phillips JM, Hallmayer JF, Hardan AY. Plasma oxytocin concentrations and OXTR polymorphisms predict social impairments in children with and without autism spectrum disorder. *Proc Natl Acad Sci USA* 111: 12258–12263, 2014. doi:10.1073/pnas.1402236111.

803. Passoni I, Leonzino M, Gigliucci V, Chini B, Busnelli M. Carbetocin is a functional selective Gq agonist that does not promote oxytocin receptor recycling after inducing beta-arrestin-independent internalisation. *J Neuroendocrinol* 28: 2016. doi:10.1111/jne.12363.

804. Patchev VK, Schlosser SF, Hassan AH, Almeida OF. Oxytocin binding sites in rat limbic and hypothalamic structures: site-specific modulation by adrenal and gonadal steroids. *Neuroscience* 57: 537–543, 1993. doi:10.1016/0306-4522(93)90003-X.

805. Paxinos G, Watson CR. *The Rat Brain in Stereotaxic Coordinates* (4th ed.). New York: Academic Press, 1998.

806. Pedersen CA, Boccia ML. Oxytocin maintains as well as initiates female sexual behavior: effects of a highly selective oxytocin antagonist. *Horm Behav* 41: 170–177, 2002. doi:10.1006/hbeh.2001.1736.

807. Pedersen CA, Boccia ML. Vasopressin interactions with oxytocin in the control of female sexual behavior. *Neuroscience* 139: 843–851, 2006. doi:10.1016/j.neuroscience.2006.01.002.

808. Pedersen CA, Caldwell JD, Walker C, Ayers G, Mason GA. Oxytocin activates the postpartum onset of rat maternal behavior in the ventral tegmental and medial preoptic areas. *Behav Neurosci* 108: 1163–1171, 1994. doi:10.1037/0735-7044.108.6.1163.

809. Pedersen CA, Prange AJ Jr. Induction of maternal behavior in virgin rats after intracerebroventricular administration of oxytocin. *Proc Natl Acad Sci USA* 76: 6661–6665, 1979. doi:10.1073/pnas.76.12.6661.

810. Pedersen CA, Smedley KL, Leserman J, Jarskog LF, Rau SW, Kampov-Polevoi A, Casey RL, Fender T, Garbutt JC. Intranasal oxytocin blocks alcohol withdrawal in human subjects. *Alcohol Clin Exp Res* 37: 484–489, 2013. doi:10.1111/j.1530-0277.2012.01958.x.

811. Pedersen CA, Vadlamudi SV, Boccia ML, Amico JA. Maternal behavior deficits in nulliparous oxytocin knockout mice. *Genes Brain Behav* 5: 274–281, 2006. doi:10.1111/j.1601-183X.2005.00162.x.

812. Péqueux C, Keegan BP, Hagelstein MT, Geenen V, Legros JJ, North WG. Oxytocin- and vasopressin-induced growth of human small-cell lung cancer is mediated by the mitogen-activated protein kinase pathway. *Endocr Relat Cancer* 11: 871–885, 2004. doi:10.1677/erc.1.00803.

813. Perello M, Raingo J. Leptin activates oxytocin neurons of the hypothalamic paraventricular nucleus in both control and diet-induced obese rodents. *PLoS One* 8: e59625, 2013. doi:10.1371/journal.pone.0059625.

814. Peters S, Slattery DA, Flor PJ, Neumann ID, Reber SO. Differential effects of baclofen and oxytocin on the increased ethanol consumption following chronic psychosocial stress in mice. *Addict Biol* 18: 66–77, 2013. doi:10.1111/adb.12001.

815. Peters S, Slattery DA, Uschold-Schmidt N, Reber SO, Neumann ID. Dose-dependent effects of chronic central infusion of oxytocin on anxiety, oxytocin receptor binding and stress-related parameters in mice. *Psychoneuroendocrinology* 42: 225–236, 2014. doi:10.1016/j.psyneuen.2014.01.021.

816. Peters ST, Bowen MT, Bohrer K, McGregor IS, Neumann ID. Oxytocin inhibits ethanol consumption and ethanol-induced dopamine release in the nucleus accumbens. *Addict Biol* 22: 702–711, 2017. doi:10.1111/adb.12362.

817. Petersson M, Eklund M, Uvnäs-Moberg K. Oxytocin decreases corticosterone and nociception and increases motor activity in OVX rats. *Maturitas* 51: 426–433, 2005. doi:10.1016/j.maturitas.2004.10.005.

818. Petersson M, Uvnäs-Moberg K. Systemic oxytocin treatment modulates glucocorticoid and mineralocorticoid receptor mRNA in the rat hippocampus. *Neurosci Lett* 343: 97–100, 2003. doi:10.1016/S0304-3940(03)00334-3.

819. Petrovic P, Kalisch R, Singer T, Dolan RJ. Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity. *J Neurosci* 28: 6607–6615, 2008. doi:10.1523/JNEUROSCI.4572-07.2008.

820. Pfaus JG. Pathways of sexual desire. *J Sex Med* 6: 1506–1533, 2009. doi:10.1111/j.1743-6109.2009.01309.x.

821. Pfaus JG, Smith WJ, Byrne N, Stephens G. Appetitive and consummatory sexual behaviors of female rats in bilevel chambers. II. Patterns of estrus termination following vaginocervical stimulation. *Horm Behav* 37: 96–107, 2000. doi:10.1006/hbeh.1999.1562.

822. Phie J, Haleagrahara N, Newton P, Constantinoiu C, Sarnyai Z, Chilton L, Kinobe R. Prolonged subcutaneous administration of oxytocin accelerates angiotensin II-induced hypertension and renal damage in male rats. *PLoS One* 10: e0138048, 2015. doi:10.1371/journal.pone.0138048.

823. Pierrehumbert B, Torrisi R, Ansermet F, Borghini A, Halfon O. Adult attachment representations predict cortisol and oxytocin responses to stress. *Attach Hum Dev* 14: 453–476, 2012. doi:10.1080/14616734.2012.706394.

824. Pierrehumbert B, Torrisi R, Laufer D, Halfon O, Ansermet F, Beck Popovic M. Oxytocin response to an experimental psychosocial challenge in adults exposed to traumatic experiences during childhood or adolescence. *Neuroscience* 166: 168–177, 2010. doi:10.1016/j.neuroscience.2009.12.016.

825. Pierzynski P, Lemancewicz A, Reinheimer T, Akerlund M, Laudanski T. Inhibitory effect of barusiban and atosiban on oxytocin-induced contractions of myometrium from preterm and term pregnant women. *J Soc Gynecol Investig* 11: 384–387, 2004. doi:10.1016/j.jsgi.2004.02.008.

826. Pitman RK, Orr SP, Lasko NB. Effects of intranasal vasopressin and oxytocin on physiologic responding during personal combat imagery in Vietnam veterans with posttraumatic stress disorder. *Psychiatry Res* 48: 107–117, 1993. doi:10.1016/0165-1781(93)90035-F.

827. Pitts AF, Samuelson SD, Meller WH, Bissette G, Nemeroff CB, Kathol RG. Cerebrospinal fluid corticotropin-releasing hormone, vasopressin, and oxytocin concentrations in treated patients with major depression and controls. *Biol Psychiatry* 38: 330–335, 1995. doi:10.1016/0006-3223(95)00229-A.

828. Plotsky PM, Meaney MJ. Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. *Brain Res Mol Brain Res* 18: 195–200, 1993. doi:10.1016/0169-328X(93)90189-V.

829. Polston EK, Centorino KM, Erskine MS. Diurnal fluctuations in mating-induced oxytocinergic activity within the paraventricular and supraoptic nuclei do not influence prolactin secretion. *Endocrinology* 139: 4849–4859, 1998. doi:10.1210/endo.139.12.6341.

830. Pont JN, McArdle CA, López Bernal A. Oxytocin-stimulated NFAT transcriptional activation in human myometrial cells. *Mol Endocrinol* 26: 1743–1756, 2012. doi:10.1210/me.2012-1057.

831. Popik P, Vetulani J. Opposite action of oxytocin and its peptide antagonists on social memory in rats. *Neuropeptides* 18: 23–27, 1991. doi:10.1016/0143-4179(91)90159-G.

832. Popik P, Vetulani J, van Ree JM. Low doses of oxytocin facilitate social recognition in rats. *Psychopharmacology (Berl)* 106: 71–74, 1992. doi:10.1007/BF02253591.

833. Popik P, Vos PE, Van Ree JM. Neurohypophyseal hormone receptors in the septum are implicated in social recognition in the rat. *Behav Pharmacol* 3: 351–358, 1992. doi:10.1097/00008877-199208000-00011.

834. Postina R, Kojro E, Fahrenholz F. Separate agonist and peptide antagonist binding sites of the oxytocin receptor defined by their transfer into the V2 vasopressin receptor. *J Biol Chem* 271: 31593–31601, 1996. doi:10.1074/jbc.271.49.31593.

835. Potthoff MJ, Olson EN. MEF2: a central regulator of diverse developmental programs. *Development* 134: 4131–4140, 2007. doi:10.1242/dev.008367.

836. Poulain D, Dufy B, Vincent JD. [Proceedings: Unit activity of hypothalamic neurons antidromically located in non-anesthetized rabbits]. *J Physiol (Paris)* 67: 355A, 1973.

837. Poulain DA, Wakerley JB. Electrophysiology of hypothalamic magnocellular neurones secreting oxytocin and vasopressin. *Neuroscience* 7: 773–808, 1982. doi:10.1016/0306-4522(82)90044-6.

838. Pow DV, Morris JF. Dendrites of hypothalamic magnocellular neurons release neurohypophysial peptides by exocytosis. *Neuroscience* 32: 435–439, 1989. doi:10.1016/0306-4522(89)90091-2.

839. Prakash BS, Metten M, Schams D, Wuttke W. Development of a sensitive enzymeimmunoassay for oxytocin determination in bovine plasma. *Anim Reprod Sci* 51: 185–194, 1998. doi:10.1016/S0378-4320(98)00069-4.

840. Pratt M, Apter-Levi Y, Vakart A, Feldman M, Fishman R, Feldman T, Zagoory-Sharon O, Feldman R. Maternal depression and child oxytocin response; moderation by maternal oxytocin and relational behavior. *Depress Anxiety* 32: 635–646, 2015. doi:10.1002/da.22392.

841. Preston SD, de Waal FB. Empathy: Its ultimate and proximate bases. *Behav Brain Sci* 25: 1–20, 2002.

842. Prole DL, Taylor CW. Inositol 1,4,5-trisphosphate receptors and their protein partners as signalling hubs. *J Physiol* 594: 2849–2866, 2016. doi:10.1113/JP271139.

843. Puglia MH, Lillard TS, Morris JP, Connelly JJ. Epigenetic modification of the oxytocin receptor gene influences the perception of anger and fear in the human brain. *Proc Natl Acad Sci USA* 112: 3308–3313, 2015. doi:10.1073/pnas.1422096112.

844. Pupier S, Leveque C, Marqueze B, Kataoka M, Takahashi M, Seagar MJ. Cysteine string proteins associated with secretory granules of the rat neurohypophysis. *J Neurosci* 17: 2722–2727, 1997.

845. Purba JS, Hofman MA, Swaab DF. Decreased number of oxytocin-immunoreactive neurons in the paraventricular nucleus of the hypothalamus in Parkinson's disease. *Neurology* 44: 84–89, 1994. doi:10.1212/WNL.44.1.84.

846. Purba JS, Hoogendijk WJ, Hofman MA, Swaab DF. Increased number of vasopressin- and oxytocin-expressing neurons in the paraventricular nucleus of the hypothalamus in depression. *Arch Gen Psychiatry* 53: 137–143, 1996. doi:10.1001/archpsyc.1996.01830020055007.

847. Qi J, Yang JY, Song M, Li Y, Wang F, Wu CF. Inhibition by oxytocin of methamphetamine-induced hyperactivity related to dopamine turnover in the mesolimbic region in mice. *Naunyn Schmiedebergs Arch Pharmacol* 376: 441–448, 2008. doi:10.1007/s00210-007-0245-8.

848. Qi J, Yang JY, Wang F, Zhao YN, Song M, Wu CF. Effects of oxytocin on methamphetamine-induced conditioned place preference and the possible role of glutamatergic neurotransmission in the medial prefrontal cortex of mice in reinstatement. *Neuropharmacology* 56: 856–865, 2009. doi:10.1016/j.neuropharm.2009.01.010.

849. Quiñones-Jenab V, Jenab S, Ogawa S, Adan RA, Burbach JP, Pfaff DW. Effects of estrogen on oxytocin receptor messenger ribonucleic acid expression in the uterus, pituitary, and forebrain of the female rat. *Neuroendocrinology* 65: 9–17, 1997. doi:10.1159/000127160.

850. Quirin M, Kuhl J, Düsing R. Oxytocin buffers cortisol responses to stress in individuals with impaired emotion regulation abilities. *Psychoneuroendocrinology* 36: 898–904, 2011. doi:10.1016/j.psyneuen.2010.12.005.

851. Quirk GJ, Paré D, Richardson R, Herry C, Monfils MH, Schiller D, Vicentic A. Erasing fear memories with extinction training. *J Neurosci* 30: 14993–14997, 2010. doi:10.1523/JNEUROSCI.4268-10.2010.

852. Ragnauth AK, Devidze N, Moy V, Finley K, Goodwillie A, Kow LM, Muglia LJ, Pfaff DW. Female oxytocin gene-knockout mice, in a semi-natural environment, display exaggerated aggressive behavior. *Genes Brain Behav* 4: 229–239, 2005. doi:10.1111/j.1601-183X.2005.00118.x.

853. Ramos JW, Townsend DA, Piarulli D, Kolata S, Light K, Hale G, Matzel LD. Deletion of PEA-15 in mice is associated with specific impairments of spatial learning abilities. *BMC Neurosci* 10: 134, 2009. doi:10.1186/1471-2202-10-134.

854. Reber SO, Birkeneder L, Veenema AH, Obermeier F, Falk W, Straub RH, Neumann ID. Adrenal insufficiency and colonic inflammation after a novel chronic psychosocial stress paradigm in mice: implications and mechanisms. *Endocrinology* 148: 670–682, 2007. doi:10.1210/en.2006-0983.

855. Reber SO, Neumann ID. Defensive behavioral strategies and enhanced state anxiety during chronic subordinate colony housing are accompanied by reduced hypothalamic vasopressin, but not oxytocin, expression. *Ann N Y Acad Sci* 1148: 184–195, 2008. doi:10.1196/annals.1410.003.

856. Reinheimer TM. Barusiban suppresses oxytocin-induced preterm labour in non-human primates. *BMC Pregnancy Childbirth* 7, Suppl 1: S15, 2007. doi:10.1186/1471-2393-7-S1-S15.

857. Reinheimer TM, Bee WH, Resendez JC, Meyer JK, Haluska GJ, Chellman GJ. Barusiban, a new highly potent and long-acting oxytocin antagonist: pharmacokinetic and pharmacodynamic comparison with atosiban in a cynomolgus monkey model of preterm labor. *J Clin Endocrinol Metab* 90: 2275–2281, 2005. doi:10.1210/jc.2004-2120.

858. Ren D, Lu G, Moriyama H, Mustoe AC, Harrison EB, French JA. Genetic diversity in oxytocin ligands and receptors in New World monkeys. *PLoS One* 10: e0125775, 2015. doi:10.1371/journal.pone.0125775.

859. Renaud LP, Tang M, McCann MJ, Stricker EM, Verbalis JG. Cholecystokinin and gastric distension activate oxytocinergic cells in rat hypothalamus. *Am J Physiol Regul Integr Comp Physiol* 253: R661–R665, 1987.

860. Renthal NE, Chen CC, Williams KC, Gerard RD, Prange-Kiel J, Mendelson CR. miR-200 family and targets, ZEB1 and ZEB2, modulate uterine quiescence and contractility during pregnancy and labor. *Proc Natl Acad Sci USA* 107: 20828–20833, 2010. doi:10.1073/pnas.1008301107.

861. Reuter M, Montag C, Altmann S, Bendlow F, Elger C, Kirsch P, Becker A, Schoch-McGovern S, Simon M, Weber B, Felten A. Functional characterization of an oxytocin receptor gene variant (rs2268498) previously associated with social cognition by expression analysis in vitro and in human brain biopsy. *Soc Neurosci* 12: 604–611, 2017. doi:10.1080/17470919.2016.1214174.

862. Reversi A, Cassoni P, Chini B. Oxytocin receptor signaling in myoepithelial and cancer cells. *J Mammary Gland Biol Neoplasia* 10: 221–229, 2005. doi:10.1007/s10911-005-9583-7.

863. Reversi A, Rimoldi V, Brambillasca S, Chini B. Effects of cholesterol manipulation on the signaling of the human oxytocin receptor. *Am J Physiol Regul Integr Comp Physiol* 291: R861–R869, 2006. doi:10.1152/ajpregu.00333.2006.

864. Reversi A, Rimoldi V, Marrocco T, Cassoni P, Bussolati G, Parenti M, Chini B. The oxytocin receptor antagonist atosiban inhibits cell growth via a "biased agonist" mechanism. *J Biol Chem* 280: 16311–16318, 2005. doi:10.1074/jbc.M409945200.

865. Rhee SG. Regulation of phosphoinositide-specific phospholipase C. *Annu Rev Biochem* 70: 281–312, 2001. doi:10.1146/annurev.biochem.70.1.281.

866. Rhodes CH, Morrell JI, Pfaff DW. Immunohistochemical analysis of magnocellular elements in rat hypothalamus: distribution and numbers of cells containing neurophysin, oxytocin, and vasopressin. *J Comp Neurol* 198: 45–64, 1981. doi:10.1002/cne.901980106.

867. Rich ME, deCárdenas EJ, Lee HJ, Caldwell HK. Impairments in the initiation of maternal behavior in oxytocin receptor knockout mice. *PLoS One* 9: e98839, 2014. doi:10.1371/journal.pone.0098839.

868. Richard S, Zingg HH. The human oxytocin gene promoter is regulated by estrogens. *J Biol Chem* 265: 6098–6103, 1990.

869. Richter D. Molecular events in expression of vasopressin and oxytocin and their cognate receptors. *Am J Renal Fluid Electrolyte Physiol* 255: F207–F219, 1988.

870. Riddell DC, Mallonee R, Phillips JA, Parks JS, Sexton LA, Hamerton JL. Chromosomal assignment of human sequences encoding arginine vasopressin-neurophysin II and growth hormone releasing factor. *Somat Cell Mol Genet* 11: 189–195, 1985. doi:10.1007/BF01534707.

871. Riley PR, Flint AP, Abayasekara DR, Stewart HJ. Structure and expression of an ovine endometrial oxytocin receptor cDNA. *J Mol Endocrinol* 15: 195–202, 1995. doi:10.1677/jme.0.0150195.

872. Rimmele U, Hediger K, Heinrichs M, Klaver P. Oxytocin makes a face in memory familiar. *J Neurosci* 29: 38–42, 2009. doi:10.1523/JNEUROSCI.4260-08.2009.

873. Rinaman L. Oxytocinergic inputs to the nucleus of the solitary tract and dorsal motor nucleus of the vagus in neonatal rats. *J Comp Neurol* 399: 101–109, 1998. doi:10.1002/(SICI)1096-9861(19980914)399:1<101::AID-CNE8>3.0.CO;2-5.

874. Ring RH, Malberg JE, Potestio L, Ping J, Boikess S, Luo B, Schechter LE, Rizzo S, Rahman Z, Rosenzweig-Lipson S. Anxiolytic-like activity of oxytocin in male mice: behavioral and autonomic evidence, therapeutic implications. *Psychopharmacology (Berl)* 185: 218–225, 2006. doi:10.1007/s00213-005-0293-z.

875. Ring RH, Schechter LE, Leonard SK, Dwyer JM, Platt BJ, Graf R, Grauer S, Pulicicchio C, Resnick L, Rahman Z, Sukoff Rizzo SJ, Luo B, Beyer CE, Logue SF, Marquis KL, Hughes ZA, Rosenzweig-Lipson S. Receptor and behavioral pharmacology of WAY-267464, a non-peptide oxytocin receptor agonist. *Neuropharmacology* 58: 69–77, 2010. doi:10.1016/j.neuropharm.2009.07.016.

876. Ripamonti S, Ambrozkiewicz MC, Guzzi F, Gravati M, Biella G, Bormuth I, Hammer M, Tuffy LP, Sigler A, Kawabe H, Nishimori K, Toselli M, Brose N, Parenti M, Rhee J. Transient oxytocin signaling primes the development and function of excitatory hippocampal neurons. *eLife* 6: e22466, 2017. doi:10.7554/eLife.22466.

877. Robinson C, Schumann R, Zhang P, Young RC. Oxytocin-induced desensitization of the oxytocin receptor. *Am J Obstet Gynecol* 188: 497–502, 2003. doi:10.1067/mob.2003.22.

878. Robinson KJ, Hazon N, Lonergan M, Pomeroy PP. Validation of an enzyme-linked immunoassay (ELISA) for plasma oxytocin in a novel mammal species reveals potential errors induced by sampling procedure. *J Neurosci Methods* 226: 73–79, 2014. doi:10.1016/j.jneumeth.2014.01.019.

879. Rodrigues SM, Saslow LR, Garcia N, John OP, Keltner D. Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. *Proc Natl Acad Sci USA* 106: 21437–21441, 2009. doi:10.1073/pnas.0909579106.

880. Rodríguez J, Crespo P. Working without kinase activity: phosphotransfer-independent functions of extracellular signal-regulated kinases. *Sci Signal* 4: re3, 2011. doi:10.1126/scisignal.2002324.

881. Rogers RC, Hermann GE. Oxytocin, oxytocin antagonist, TRH, and hypothalamic paraventricular nucleus stimulation effects on gastric motility. *Peptides* 8: 505–513, 1987. doi:10.1016/0196-9781(87)90017-9.

882. Romeo RD, Mueller A, Sisti HM, Ogawa S, McEwen BS, Brake WG. Anxiety and fear behaviors in adult male and female C57BL/6 mice are modulated by maternal separation. *Horm Behav* 43: 561–567, 2003. doi:10.1016/S0018-506X(03)00063-1.

883. Romero-Fernandez W, Borroto-Escuela DO, Agnati LF, Fuxe K. Evidence for the existence of dopamine D2-oxytocin receptor heteromers in the ventral and dorsal striatum with facilitatory receptor-receptor interactions. *Mol Psychiatry* 18: 849–850, 2013. doi:10.1038/mp.2012.103.

884. Romero T, Nagasawa M, Mogi K, Hasegawa T, Kikusui T. Oxytocin promotes social bonding in dogs. *Proc Natl Acad Sci USA* 111: 9085–9090, 2014. doi:10.1073/pnas.1322868111.

885. Ross HE, Cole CD, Smith Y, Neumann ID, Landgraf R, Murphy AZ, Young LJ. Characterization of the oxytocin system regulating affiliative behavior in female prairie voles. *Neuroscience* 162: 892–903, 2009. doi:10.1016/j.neuroscience.2009.05.055.

886. Ross HE, Freeman SM, Spiegel LL, Ren X, Terwilliger EF, Young LJ. Variation in oxytocin receptor density in the nucleus accumbens has differential effects on affiliative behaviors in monogamous and polygamous voles. *J Neurosci* 29: 1312–1318, 2009. doi:10.1523/JNEUROSCI.5039-08.2009.

887. Ross HE, Young LJ. Oxytocin and the neural mechanisms regulating social cognition and affiliative behavior. *Front Neuroendocrinol* 30: 534–547, 2009. doi:10.1016/j.yfrne.2009.05.004.

888. Roux PP, Blenis J. ERK and p38 MAPK-activated protein kinases: a family of protein kinases with diverse biological functions. *Microbiol Mol Biol Rev* 68: 320–344, 2004. doi:10.1128/MMBR.68.2.320-344.2004.

889. Rozen F, Russo C, Banville D, Zingg HH. Structure, characterization, and expression of the rat oxytocin receptor gene. *Proc Natl Acad Sci USA* 92: 200–204, 1995. doi:10.1073/pnas.92.1.200.

890. Russell JA, Neumann I, Landgraf R. Oxytocin and vasopressin release in discrete brain areas after naloxone in morphine-tolerant and -dependent anesthetized rats: push-pull perfusion study. *J Neurosci* 12: 1024–1032, 1992.

891. Rutigliano G, Rocchetti M, Paloyelis Y, Gilleen J, Sardella A, Cappucciati M, Palombini E, Dell'Osso L, Caverzasi E, Politi P, McGuire P, Fusar-Poli P. Peripheral oxytocin and vasopressin: Biomarkers of psychiatric disorders? A comprehensive systematic review and preliminary meta-analysis. *Psychiatry Res* 241: 207–220, 2016. doi:10.1016/j.psychres.2016.04.117.

892. Rydén G, Sjöholm I. Half-life of oxytocin in blood of pregnant and non-pregnant women. *Acta Endocrinol (Copenh)* 61: 425–431, 1969.

893. Sabatier N, Caquineau C, Dayanithi G, Bull P, Douglas AJ, Guan XM, Jiang M, Van der Ploeg L, Leng G. Alpha-melanocyte-stimulating hormone stimulates oxytocin release from the dendrites of hypothalamic neurons while inhibiting oxytocin release from their terminals in the neurohypophysis. *J Neurosci* 23: 10351–10358, 2003.

894. Sabatier N, Leng G, Menzies J. Oxytocin, feeding, and satiety. *Front Endocrinol (Lausanne)* 4: 35, 2013. doi:10.3389/fendo.2013.00035.

895. Sabihi S, Dong SM, Durosko NE, Leuner B. Oxytocin in the medial prefrontal cortex regulates maternal care, maternal aggression and anxiety during the postpartum period. *Front Behav Neurosci* 8: 258, 2014. doi:10.3389/fnbeh.2014.00258.

896. Sabihi S, Durosko NE, Dong SM, Leuner B. Oxytocin in the prelimbic medial prefrontal cortex reduces anxiety-like behavior in female and male rats. *Psychoneuroendocrinology* 45: 31–42, 2014. doi:10.1016/j.psyneuen.2014.03.009.

897. Sachidanandan D, Reddy HP, Mani A, Hyde GJ, Bera AK. The neuropeptide Orexin-A inhibits the GABAA receptor by PKC and Ca2+/CaMKII-dependent phosphorylation of its beta1 subunit. *J Mol Neurosci* 61: 459–467, 2017. doi:10.1007/s12031-017-0886-0.

898. Sala M, Braida D, Donzelli A, Martucci R, Busnelli M, Bulgheroni E, Rubino T, Parolaro D, Nishimori K, Chini B. Mice heterozygous for the oxytocin receptor gene (Oxtr(+/−)) show impaired social behaviour but not increased aggression or cognitive inflexibility: evidence of a selective haploinsufficiency gene effect. *J Neuroendocrinol* 25: 107–118, 2013. doi:10.1111/j.1365-2826.2012.02385.x.

899. Sala M, Braida D, Lentini D, Busnelli M, Bulgheroni E, Capurro V, Finardi A, Donzelli A, Pattini L, Rubino T, Parolaro D, Nishimori K, Parenti M, Chini B. Pharmacologic rescue of impaired cognitive flexibility, social deficits, increased aggression, and seizure susceptibility in oxytocin receptor null mice: a neurobehavioral model of autism. *Biol Psychiatry* 69: 875–882, 2011. doi:10.1016/j.biopsych.2010.12.022.

900. Saleem H, Tovey SC, Rahman T, Riley AM, Potter BV, Taylor CW. Stimulation of inositol 1,4,5-trisphosphate (IP3) receptor subtypes by analogues of IP3. *PLoS One* 8: e54877, 2013. doi:10.1371/journal.pone.0054877.

901. Salvatore CA, Woyden CJ, Guidotti MT, Pettibone DJ, Jacobson MA. Cloning and expression of the rhesus monkey oxytocin receptor. *J Recept Signal Transduct Res* 18: 15–24, 1998. doi:10.3109/10799899809039162.

902. Sanborn BM. Hormonal signaling and signal pathway crosstalk in the control of myometrial calcium dynamics. *Semin Cell Dev Biol* 18: 305–314, 2007. doi:10.1016/j.semcdb.2007.05.007.

903. Sanborn BM, Dodge K, Monga M, Qian A, Wang W, Yue C. Molecular mechanisms regulating the effects of oxytocin on myometrial intracellular calcium. *Adv Exp Med Biol* 449: 277–286, 1998. doi:10.1007/978-1-4615-4871-3_35.

904. Sanborn BM, Qian A, Ku CY, Wen Y, Anwer K, Monga M, Singh SP. Mechanisms regulating oxytocin receptor coupling to phospholipase C in rat and human myometrium. *Adv Exp Med Biol* 395: 469–479, 1995.

905. Sánchez-Fernández G, Cabezudo S, Caballero Á, García-Hoz C, Tall GG, Klett J, Michnick SW, Mayor F Jr, Ribas C. Protein kinase C zeta interacts with a novel binding region of galphaq to act as a functional effector. *J Biol Chem* 291: 9513–9525, 2016. doi:10.1074/jbc.M115.684308.

906. Sánchez-Vidaña DI, Chan NM, Chan AH, Hui KK, Lee S, Chan HY, Law YS, Sze MY, Tsui WC, Fung TK, Lau BW, Lai CY. Repeated treatment with oxytocin promotes hippocampal cell proliferation, dendritic maturation and affects socio-emotional behavior. *Neuroscience* 333: 65–77, 2016. doi:10.1016/j.neuroscience.2016.07.005.

907. Sarnyai Z, Kovács GL. Role of oxytocin in the neuroadaptation to drugs of abuse. *Psychoneuroendocrinology* 19: 85–117, 1994. doi:10.1016/0306-4530(94)90062-0.

908. Sarnyai Z, Szabó G, Kovács GL, Telegdy G. Opposite actions of oxytocin and vasopressin in the development of cocaine-induced behavioral sensitization in mice. *Pharmacol Biochem Behav* 43: 491–494, 1992. doi:10.1016/0091-3057(92)90182-F.

909. Sasaki T, Takemori H, Yagita Y, Terasaki Y, Uebi T, Horike N, Takagi H, Susumu T, Teraoka H, Kusano K, Hatano O, Oyama N, Sugiyama Y, Sakoda S, Kitagawa K. SIK2 is a key regulator for neuronal survival after ischemia via TORC1-CREB. *Neuron* 69: 106–119, 2011. doi:10.1016/j.neuron.2010.12.004.

910. Satake H, Takuwa K, Minakata H, Matsushima O. Evidence for conservation of the vasopressin/oxytocin superfamily in Annelida. *J Biol Chem* 274: 5605–5611, 1999. doi:10.1074/jbc.274.9.5605.

911. Savaskan E, Ehrhardt R, Schulz A, Walter M, Schächinger H. Post-learning intranasal oxytocin modulates human memory for facial identity. *Psychoneuroendocrinology* 33: 368–374, 2008. doi:10.1016/j.psyneuen.2007.12.004.

912. Sawchenko PE, Swanson LW, Joseph SA. The distribution and cells of origin of ACTH(1–39)-stained varicosities in the paraventricular and supraoptic nuclei. *Brain Res* 232: 365–374, 1982. doi:10.1016/0006-8993(82)90280-3.

913. Scantamburlo G, Hansenne M, Fuchs S, Pitchot W, Maréchal P, Pequeux C, Ansseau M, Legros JJ. Plasma oxytocin levels and anxiety in patients with major depression. *Psychoneuroendocrinology* 32: 407–410, 2007. doi:10.1016/j.psyneuen.2007.01.009.

914. Schafer EA, MacKenzie KF. The action of animal extracts on milk secretion. *Proc R Soc Lond, B* 84: 16–22, 1911. doi:10.1098/rspb.1911.0042.

915. Scharrer E. Die Lichtempfindlichkeit Blinder Elritzen. (Untersuchungen Über Das Zwischenhirn Der Fische I). *Z Vgl Physiol* 7: 1–38, 1928. doi:10.1007/BF00341151.

916. Scharrer E, Scharrer B. Über Drüsen-Nervenzellen Und Neurosekretorische Organe Bei Wirbellosen Und Wirbeltieren. *Biol Rev Camb Philos Soc* 12: 185–216, 1937. doi:10.1111/j.1469-185X.1937.tb01229.x.

917. Scheele D, Striepens N, Güntürkün O, Deutschländer S, Maier W, Kendrick KM, Hurlemann R. Oxytocin modulates social distance between males and females. *J Neurosci* 32: 16074–16079, 2012. doi:10.1523/JNEUROSCI.2755-12.2012.

918. Scheele D, Wille A, Kendrick KM, Stoffel-Wagner B, Becker B, Güntürkün O, Maier W, Hurlemann R. Oxytocin enhances brain reward system responses in men viewing the face of their female partner. *Proc Natl Acad Sci USA* 110: 20308–20313, 2013. doi:10.1073/pnas.1314190110.

919. Schneiderman I, Zagoory-Sharon O, Leckman JF, Feldman R. Oxytocin during the initial stages of romantic attachment: relations to couples' interactive reciprocity. *Psychoneuroendocrinology* 37: 1277–1285, 2012. doi:10.1016/j.psyneuen.2011.12.021.

920. Schorscher-Petcu A, Dupré A, Tribollet E. Distribution of vasopressin and oxytocin binding sites in the brain and upper spinal cord of the common marmoset. *Neurosci Lett* 461: 217–222, 2009. doi:10.1016/j.neulet.2009.06.016.

921. Schülke O, Bhagavatula J, Vigilant L, Ostner J. Social bonds enhance reproductive success in male macaques. *Curr Biol* 20: 2207–2210, 2010. doi:10.1016/j.cub.2010.10.058.

922. Schumacher M, Coirini H, Pfaff DW, McEwen BS. Behavioral effects of progesterone associated with rapid modulation of oxytocin receptors. *Science* 250: 691–694, 1990. doi:10.1126/science.2173139.

922a. Scott N, Prigge M, Yizhar O, Kimchi T. A sexually dimorphic hypothalamic circuit controls maternal care and oxytocin secretion. *Nature* 525: 519–522, 2015.

923. Screaton RA, Conkright MD, Katoh Y, Best JL, Canettieri G, Jeffries S, Guzman E, Niessen S, Yates JR III, Takemori H, Okamoto M, Montminy M. The CREB coactivator TORC2 functions as a calcium- and cAMP-sensitive coincidence detector. *Cell* 119: 61–74, 2004. doi:10.1016/j.cell.2004.09.015.

924. Selvage DJ, Johnston CA. Interaction between norepinephrine, oxytocin, and nitric oxide in the stimulation of gonadotropin-releasing hormone release from proestrous rat basal hypothalamus explants. *J Neuroendocrinol* 16: 819–824, 2004. doi:10.1111/j.1365-2826.2004.01235.x.

925. Seyfarth RM, Cheney DL. The evolutionary origins of friendship. *Annu Rev Psychol* 63: 153–177, 2012. doi:10.1146/annurev-psych-120710-100337.

926. Shahrokh DK, Zhang TY, Diorio J, Gratton A, Meaney MJ. Oxytocin-dopamine interactions mediate variations in maternal behavior in the rat. *Endocrinology* 151: 2276–2286, 2010. doi:10.1210/en.2009-1271.

927. Shalizi AK, Bonni A. brawn for brains: the role of MEF2 proteins in the developing nervous system. *Curr Top Dev Biol* 69: 239–266, 2005. doi:10.1016/S0070-2153(05)69009-6.

928. Sharifullina E, Nistri A. Glutamate uptake block triggers deadly rhythmic bursting of neonatal rat hypoglossal motoneurons. *J Physiol* 572: 407–423, 2006. doi:10.1113/jphysiol.2005.100412.

929. Sharma D, Handa RJ, Uht RM. The ERβ ligand 5α-androstane, 3β,17β-diol (3β-diol) regulates hypothalamic oxytocin (Oxt) gene expression. *Endocrinology* 153: 2353–2361, 2012. doi:10.1210/en.2011-1002.

930. Shikama Y, Kato T, Nagaoka U, Hosoya T, Katagiri T, Yamaguchi K, Sasaki H. Localization of the gustatory pathway in the human midbrain. *Neurosci Lett* 218: 198–200, 1996. doi:10.1016/S0304-3940(96)13137-2.

931. Shinghal R, Barnes A, Mahar KM, Stier B, Giancaterino L, Condreay LD, Black L, McCallum SW. Safety and efficacy of epelsiban in the treatment of men with premature ejaculation: a randomized, double-blind, placebo-controlled, fixed-dose study. *J Sex Med* 10: 2506–2517, 2013. doi:10.1111/jsm.12272.

932. Shlykov SG, Yang M, Alcorn JL, Sanborn BM. Capacitative cation entry in human myometrial cells and augmentation by hTrpC3 overexpression. *Biol Reprod* 69: 647–655, 2003. doi:10.1095/biolreprod.103.015396.

933. Shor-Posner G, Azar AP, Insinga S, Leibowitz SF. Deficits in the control of food intake after hypothalamic paraventricular nucleus lesions. *Physiol Behav* 35: 883–890, 1985. doi:10.1016/0031-9384(85)90255-0.

934. Shu Q, Zhang J, Ma W, Lei Y, Zhou D. Orexin-A promotes Glu uptake by OX1R/PKCα/ERK1/2/GLT-1 pathway in astrocytes and protects co-cultured astrocytes and neurons against apoptosis in anoxia/hypoglycemic injury in vitro. *Mol Cell Biochem* 425: 103–112, 2017. doi:10.1007/s11010-016-2866-z.

935. Silk JB, Alberts SC, Altmann J. Social bonds of female baboons enhance infant survival. *Science* 302: 1231–1234, 2003. doi:10.1126/science.1088580.

936. Silk JB, Beehner JC, Bergman TJ, Crockford C, Engh AL, Moscovice LR, Wittig RM, Seyfarth RM, Cheney DL. Strong and consistent social bonds enhance the longevity of female baboons. *Curr Biol* 20: 1359–1361, 2010. doi:10.1016/j.cub.2010.05.067.

937. Simmons JP, Nelson LD, Simonsohn U. False-positive psychology: undisclosed flexibility in data collection and analysis allows presenting anything as significant. *Psychol Sci* 22: 1359–1366, 2011. doi:10.1177/0956797611417632.

938. Simmons ML, Terman GW, Gibbs SM, Chavkin C. L-type calcium channels mediate dynorphin neuropeptide release from dendrites but not axons of hippocampal granule cells. *Neuron* 14: 1265–1272, 1995. doi:10.1016/0896-6273(95)90273-2.

939. Simpson EA, Paukner A, Sclafani V, Kaburu SS, Suomi SJ, Ferrari PF. Acute oxytocin improves memory and gaze following in male but not female nursery-reared infant macaques. *Psychopharmacology (Berl)* 234: 497–506, 2017. doi:10.1007/s00213-016-4480-x.

940. Simpson K, Parker J, Plumer J, Bloom S. CCK, PYY and PP: the control of energy balance. *Handb Exp Pharmacol* 209: 209–230, 2012. doi:10.1007/978-3-642-24716-3_9.

941. Sims JS, Lorden JF. Effect of paraventricular nucleus lesions on body weight, food intake and insulin levels. *Behav Brain Res* 22: 265–281, 1986. doi:10.1016/0166-4328(86)90071-9.

942. Sinclair MS, Perea-Martinez I, Dvoryanchikov G, Yoshida M, Nishimori K, Roper SD, Chaudhari N. Oxytocin signaling in mouse taste buds. *PLoS One* 5: e11980, 2010. doi:10.1371/journal.pone.0011980.

943. Singewald N, Schmuckermair C, Whittle N, Holmes A, Ressler KJ. Pharmacology of cognitive enhancers for exposure-based therapy of fear, anxiety and trauma-related disorders. *Pharmacol Ther* 149: 150–190, 2015. doi:10.1016/j.pharmthera.2014.12.004.

944. Sita LV, Elias CF, Bittencourt JC. Connectivity pattern suggests that incerto-hypothalamic area belongs to the medial hypothalamic system. *Neuroscience* 148: 949–969, 2007. doi:10.1016/j.neuroscience.2007.07.010.

945. Skuse DH, Gallagher L. Dopaminergic-neuropeptide interactions in the social brain. *Trends Cogn Sci* 13: 27–35, 2009. doi:10.1016/j.tics.2008.09.007.

946. Skuse DH, Lori A, Cubells JF, Lee I, Conneely KN, Puura K, Lehtimäki T, Binder EB, Young LJ. Common polymorphism in the oxytocin receptor gene (OXTR) is associated with human social recognition skills. *Proc Natl Acad Sci USA* 111: 1987–1992, 2014. doi:10.1073/pnas.1302985111.

947. Sladek CD, Somponpun SJ. Oestrogen receptor beta: role in neurohypophyseal neurones. *J Neuroendocrinol* 16: 365–371, 2004. doi:10.1111/j.0953-8194.2004.01187.x.

948. Slattery DA, Cryan JF. Using the rat forced swim test to assess antidepressant-like activity in rodents. *Nat Protoc* 7: 1009–1014, 2012. doi:10.1038/nprot.2012.044.

949. Slattery DA, Naik RR, Grund T, Yen YC, Sartori SB, Füchsl A, Finger BC, Elfving B, Nordemann U, Guerrini R, Calo G, Wegener G, Mathé AA, Singewald N, Czibere L, Landgraf R, Neumann ID. Selective breeding for high anxiety introduces a synonymous SNP that increases neuropeptide S receptor activity. *J Neurosci* 35: 4599–4613, 2015. doi:10.1523/JNEUROSCI.4764-13.2015.

950. Slattery DA, Neumann ID. Chronic icv oxytocin attenuates the pathological high anxiety state of selectively bred Wistar rats. *Neuropharmacology* 58: 56–61, 2010. doi:10.1016/j.neuropharm.2009.06.038.

951. Slattery DA, Neumann ID. No stress please! Mechanisms of stress hyporesponsiveness of the maternal brain. *J Physiol* 586: 377–385, 2008. doi:10.1113/jphysiol.2007.145896.

952. Smearman EL, Winiarski DA, Brennan PA, Najman J, Johnson KC. Social stress and the oxytocin receptor gene interact to predict antisocial behavior in an at-risk cohort. *Dev Psychopathol* 27: 309–318, 2015. doi:10.1017/S0954579414000649.

953. Smeltzer MD, Curtis JT, Aragona BJ, Wang Z. Dopamine, oxytocin, and vasopressin receptor binding in the medial prefrontal cortex of monogamous and promiscuous voles. *Neurosci Lett* 394: 146–151, 2006. doi:10.1016/j.neulet.2005.10.019.

954. Smith AL, Freeman SM, Voll RJ, Young LJ, Goodman MM. Investigation of an F-18 oxytocin receptor selective ligand via PET imaging. *Bioorg Med Chem Lett* 23: 5415–5420, 2013. doi:10.1016/j.bmcl.2013.07.045.

955. Smith AS, Agmo A, Birnie AK, French JA. Manipulation of the oxytocin system alters social behavior and attraction in pair-bonding primates, *Callithrix penicillata*. *Horm Behav* 57: 255–262, 2010. doi:10.1016/j.yhbeh.2009.12.004.

956. Smith AS, Tabbaa M, Lei K, Eastham P, Butler MJ, Linton L, Altshuler R, Liu Y, Wang Z. Local oxytocin tempers anxiety by activating GABAA receptors in the hypothalamic paraventricular nucleus. *Psychoneuroendocrinology* 63: 50–58, 2016. doi:10.1016/j.psyneuen.2015.09.017.

957. Smith CJ, Poehlmann ML, Li S, Ratnaseelan AM, Bredewold R, Veenema AH. Age and sex differences in oxytocin and vasopressin V1a receptor binding densities in the rat brain: focus on the social decision-making network. *Brain Struct Funct* 222: 981–1006, 2017. doi:10.1007/s00429-016-1260-7.

958. Smith J, Williams K, Birkett S, Nicholson H, Glue P, Nutt DJ. Neuroendocrine and clinical effects of electroconvulsive therapy and their relationship to treatment outcome. *Psychol Med* 24: 547–555, 1994. doi:10.1017/S0033291700027707.

959. Smith JE, Williams K, Burkett S, Glue P, Nutt DJ. Oxytocin and vasopressin responses to ECT. *Psychiatry Res* 32: 201–202, 1990. doi:10.1016/0165-1781(90)90087-L.

960. Smith MP, Ayad VJ, Mundell SJ, McArdle CA, Kelly E, López Bernal A. Internalization and desensitization of the oxytocin receptor is inhibited by Dynamin and clathrin mutants in human embryonic kidney 293 cells. *Mol Endocrinol* 20: 379–388, 2006. doi:10.1210/me.2005-0031.

961. Snoeren EM, Veening JG, Olivier B, Oosting RS. Serotonin 1A receptors and sexual behavior in female rats: a review. *Pharmacol Biochem Behav* 121: 43–52, 2014. doi:10.1016/j.pbb.2013.11.017.

962. Soares MC, Bshary R, Mendonça R, Grutter AS, Oliveira RF. Arginine vasotocin regulation of interspecific cooperative behaviour in a cleaner fish. *PLoS One* 7: e39583, 2012. doi:10.1371/journal.pone.0039583.

963. Sofroniew MV. Morphology of vasopressin and oxytocin neurones and their central and vascular projections. *Prog Brain Res* 60: 101–114, 1983. doi:10.1016/S0079-6123(08)64378-2.

964. Sofroniew MV. Projections from vasopressin, oxytocin, and neurophysin neurons to neural targets in the rat and human. *J Histochem Cytochem* 28: 475–478, 1980. doi:10.1177/28.5.7381192.

965. Soloff MS. Oxytocin receptors and mammary myoepithelial cells. *J Dairy Sci* 65: 326–337, 1982. doi:10.3168/jds.S0022-0302(82)82194-2.

966. Soloff MS, Fernstrom MA, Periyasamy S, Soloff S, Baldwin S, Wieder M. Regulation of oxytocin receptor concentration in rat uterine explants by estrogen and progesterone. *Can J Biochem Cell Biol* 61: 625–630, 1983. doi:10.1139/o83-078.

967. Son SJ, Filosa JA, Potapenko ES, Biancardi VC, Zheng H, Patel KP, Tobin VA, Ludwig M, Stern JE. Dendritic peptide release mediates interpopulation crosstalk between neurosecretory and preautonomic networks. *Neuron* 78: 1036–1049, 2013. doi:10.1016/j.neuron.2013.04.025.

968. Steinman MQ, Duque-Wilckens N, Greenberg GD, Hao R, Campi KL, Laredo SA, Laman-Maharg A, Manning CE, Doig IE, Lopez EM, Walch K, Bales KL, Trainor BC. Sex-specific effects of stress on oxytocin neurons correspond with responses to intranasal oxytocin. *Biol Psychiatry* 80: 406–414, 2016. doi:10.1016/j.biopsych.2015.10.007.

969. Sterba G. Ascending neurosecretory pathways of the peptidergic type. In: *Neurosecretion — The Final Neuroendocrine Pathway: VI International Symposium on Neurosecretion, London 1973*, edited by Knowles F, Vollrath L. Berlin, Heidelberg: Springer, 1974, p. 38–47.

970. Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: a new method for screening antidepressants in mice. *Psychopharmacology (Berl)* 85: 367–370, 1985. doi:10.1007/BF00428203.

971. Steward O, Schuman EM. Protein synthesis at synaptic sites on dendrites. *Annu Rev Neurosci* 24: 299–325, 2001. doi:10.1146/annurev.neuro.24.1.299.

972. Stojilkovic SS. Ca2+-regulated exocytosis and SNARE function. *Trends Endocrinol Metab* 16: 81–83, 2005. doi:10.1016/j.tem.2005.02.002.

973. Stoneham MD, Everitt BJ, Hansen S, Lightman SL, Todd K. Oxytocin and sexual behaviour in the male rat and rabbit. *J Endocrinol* 107: 97–106, 1985. doi:10.1677/joe.0.1070097.

974. Stoop R, Hegoburu C, van den Burg E. New opportunities in vasopressin and oxytocin research: a perspective from the amygdala. *Annu Rev Neurosci* 38: 369–388, 2015. doi:10.1146/annurev-neuro-071714-033904.

975. Strakova Z, Copland JA, Lolait SJ, Soloff MS. ERK2 mediates oxytocin-stimulated PGE2 synthesis. *Am J Physiol Endocrinol Physiol* 274: E634–E641, 1998.

976. Strakova Z, Soloff MS. Coupling of oxytocin receptor to G proteins in rat myometrium during labor: Gi receptor interaction. *Am J Physiol Endocrinol Physiol* 272: E870–E876, 1997.

977. Strathearn L, Iyengar U, Fonagy P, Kim S. Maternal oxytocin response during mother-infant interaction: associations with adult temperament. *Horm Behav* 61: 429–435, 2012. doi:10.1016/j.yhbeh.2012.01.014.

978. Striepens N, Scheele D, Kendrick KM, Becker B, Schäfer L, Schwalba K, Reul J, Maier W, Hurlemann R. Oxytocin facilitates protective responses to aversive social stimuli in males. *Proc Natl Acad Sci USA* 109: 18144–18149, 2012. doi:10.1073/pnas.1208852109.

979. Succu S, Sanna F, Melis T, Boi A, Argiolas A, Melis MR. Stimulation of dopamine receptors in the paraventricular nucleus of the hypothalamus of male rats induces penile erection and increases extra-cellular dopamine in the nucleus accumbens: Involvement of central oxytocin. *Neuropharmacology* 52: 1034–1043, 2007. doi:10.1016/j.neuropharm.2006.10.019.

980. Sumner BE, Coombes JE, Pumford KM, Russell JA. Opioid receptor subtypes in the supraoptic nucleus and posterior pituitary gland of morphine-tolerant rats. *Neuroscience* 37: 635–645, 1990. doi:10.1016/0306-4522(90)90095-L.

981. Sun P, Smith AS, Lei K, Liu Y, Wang Z. Breaking bonds in male prairie vole: long-term effects on emotional and social behavior, physiology, and neurochemistry. *Behav Brain Res* 265: 22–31, 2014. doi:10.1016/j.bbr.2014.02.016.

982. Suraev AS, Bowen MT, Ali SO, Hicks C, Ramos L, McGregor IS. Adolescent exposure to oxytocin, but not the selective oxytocin receptor agonist TGOT, increases social behavior and plasma oxytocin in adulthood. *Horm Behav* 65: 488–496, 2014. doi:10.1016/j.yhbeh.2014.03.002.

983. Swaab DF, Bao AM, Lucassen PJ. The stress system in the human brain in depression and neurodegeneration. *Ageing Res Rev* 4: 141–194, 2005. doi:10.1016/j.arr.2005.03.003.

984. Swaab DF, Purba JS, Hofman MA. Alterations in the hypothalamic paraventricular nucleus and its oxytocin neurons (putative satiety cells) in Prader-Willi syndrome: a study of five cases. *J Clin Endocrinol Metab* 80: 573–579, 1995.

985. Swanson LW, McKellar S. The distribution of oxytocin- and neurophysin-stained fibers in the spinal cord of the rat and monkey. *J Comp Neurol* 188: 87–106, 1979. doi:10.1002/cne.901880108.

986. Swanson LW, Sawchenko PE, Wiegand SJ, Price JL. Separate neurons in the paraventricular nucleus project to the median eminence and to the medulla or spinal cord. *Brain Res* 198: 190–195, 1980. doi:10.1016/0006-8993(80)90354-6.

987. Szeto A, McCabe PM, Nation DA, Tabak BA, Rossetti MA, McCullough ME, Schneiderman N, Mendez AJ. Evaluation of enzyme immunoassay and radioimmunoassay methods for the measurement of plasma oxytocin. *Psychosom Med* 73: 393–400, 2011. doi:10.1097/PSY.0b013e31821df0c2.

988. Szeto A, Sun-Suslow N, Mendez AJ, Hernandez RI, Wagner KV, McCabe PM. Regulation of the macrophage oxytocin receptor in response to inflammation. *Am J Physiol Endocrinol Metab* 312: E183–E189, 2017. doi:10.1152/ajpendo.00346.2016.

989. Takase K, Oda S, Kuroda M, Funato H. Monoaminergic and neuropeptidergic neurons have distinct expression profiles of histone deacetylases. *PLoS One* 8: e58473, 2013. doi:10.1371/journal.pone.0058473.

990. Takayanagi Y, Kasahara Y, Onaka T, Takahashi N, Kawada T, Nishimori K. Oxytocin receptor-deficient mice developed late-onset obesity. *Neuroreport* 19: 951–955, 2008. doi:10.1097/WNR.0b013e3283021ca9.

991. Takayanagi Y, Yoshida M, Bielsky IF, Ross HE, Kawamata M, Onaka T, Yanagisawa T, Kimura T, Matzuk MM, Young LJ, Nishimori K. Pervasive social deficits, but normal parturition, in oxytocin receptor-deficient mice. *Proc Natl Acad Sci USA* 102: 16096–16101, 2005. doi:10.1073/pnas.0505312102.

992. Tansey KE, Brookes KJ, Hill MJ, Cochrane LE, Gill M, Skuse D, Correia C, Vicente A, Kent L, Gallagher L, Anney RJ. Oxytocin receptor (OXTR) does not play a major role in the aetiology of autism: genetic and molecular studies. *Neurosci Lett* 474: 163–167, 2010. doi:10.1016/j.neulet.2010.03.035.

993. Tasker JG. Rapid glucocorticoid actions in the hypothalamus as a mechanism of homeostatic integration. *Obesity (Silver Spring)* 14, Suppl 5: 259S–265S, 2006. doi:10.1038/oby.2006.320.

994. Tasker JG, Di S, Malcher-Lopes R. Minireview: rapid glucocorticoid signaling via membrane-associated receptors. *Endocrinology* 147: 5549–5556, 2006. doi:10.1210/en.2006-0981.

995. Taylor AH, Whitley GS, Nussey SS. The interaction of arginine vasopressin and oxytocin with bovine adrenal medulla cells. *J Endocrinol* 121: 133–139, 1989. doi:10.1677/joe.0.1210133.

996. Taylor SE, Gonzaga GC, Klein LC, Hu P, Greendale GA, Seeman TE. Relation of oxytocin to psychological stress responses and hypothalamic-pituitary-adrenocortical axis activity in older women. *Psychosom Med* 68: 238–245, 2006. doi:10.1097/01.psy.0000203242.95990.74.

997. Terenzi MG, Ingram CD. Oxytocin-induced excitation of neurones in the rat central and medial amygdaloid nuclei. *Neuroscience* 134: 345–354, 2005. doi:10.1016/j.neuroscience.2005.04.004.

998. Terrillon S, Durroux T, Mouillac B, Breit A, Ayoub MA, Taulan M, Jockers R, Barberis C, Bouvier M. Oxytocin and vasopressin V1a and V2 receptors form constitutive homo- and heterodimers during biosynthesis. *Mol Endocrinol* 17: 677–691, 2003. doi:10.1210/me.2002-0222.

999. Terzidou V, Blanks AM, Kim SH, Thornton S, Bennett PR. Labor and inflammation increase the expression of oxytocin receptor in human amnion. *Biol Reprod* 84: 546–552, 2011. doi:10.1095/biolreprod.110.086785.

1000. Terzidou V, Lee Y, Lindström T, Johnson M, Thornton S, Bennett PR. Regulation of the human oxytocin receptor by nuclear factor-kappaB and CCAAT/enhancer-binding protein-beta. *J Clin Endocrinol Metab* 91: 2317–2326, 2006. doi:10.1210/jc.2005-2649.

1001. Terzidou V, Sooranna SR, Kim LU, Thornton S, Bennett PR, Johnson MR. Mechanical stretch up-regulates the human oxytocin receptor in primary human uterine myocytes. *J Clin Endocrinol Metab* 90: 237–246, 2005. doi:10.1210/jc.2004-0277.

1002. Theodosis DT. Oxytocin-immunoreactive terminals synapse on oxytocin neurones in the supraoptic nucleus. *Nature* 313: 682–684, 1985. doi:10.1038/313682a0.

1003. Theodosis DT. Oxytocin-secreting neurons: a physiological model of morphological neuronal and glial plasticity in the adult hypothalamus. *Front Neuroendocrinol* 23: 101–135, 2002. doi:10.1006/frne.2001.0226.

1004. Thompson RJ, Parker KJ, Hallmayer JF, Waugh CE, Gotlib IH. Oxytocin receptor gene polymorphism (rs2254298) interacts with familial risk for psychopathology to predict symptoms of depression and anxiety in adolescent girls. *Psychoneuroendocrinology* 36: 144–147, 2011. doi:10.1016/j.psyneuen.2010.07.003.

1005. Thornton S, Goodwin TM, Greisen G, Hedegaard M, Arce JC. The effect of barusiban, a selective oxytocin antagonist, in threatened preterm labor at late gestational age: a randomized, double-blind, placebo-controlled trial. *Am J Obstet Gynecol* 200: 627.e1144–627.e10, 2009. doi:10.1016/j.ajog.2009.01.015.

1006. Thornton S, Miller H, Valenzuela G, Snidow J, Stier B, Fossler MJ, Montague TH, Powell M, Beach KJ. Treatment of spontaneous preterm labour with retosiban: a phase 2 proof-of-concept study. *Br J Clin Pharmacol* 80: 740–749, 2015. doi:10.1111/bcp.12646.

1007. Tiedge H, Bloom FE, Richter D. RNA, whither goest thou? *Science* 283: 186–187, 1999. doi:10.1126/science.283.5399.186.

1008. Tobin V, Leng G, Ludwig M. The involvement of actin, calcium channels and exocytosis proteins in somato-dendritic oxytocin and vasopressin release. *Front Physiol* 3: 261, 2012. doi:10.3389/fphys.2012.00261.

1009. Tobin VA, Arechaga G, Brunton PJ, Russell JA, Leng G, Ludwig M, Douglas AJ. Oxytocinase in the female rat hypothalamus: a novel mechanism controlling oxytocin neurones during lactation. *J Neuroendocrinol* 26: 205–216, 2014. doi:10.1111/jne.12141.

1010. Tobin VA, Douglas AJ, Leng G, Ludwig M. The involvement of voltage-operated calcium channels in somato-dendritic oxytocin release. *PLoS One* 6: e25366, 2011. doi:10.1371/journal.pone.0025366.

1011. Tomizawa K, Iga N, Lu YF, Moriwaki A, Matsushita M, Li ST, Miyamoto O, Itano T, Matsui H. Oxytocin improves long-lasting spatial memory during motherhood through MAP kinase cascade. *Nat Neurosci* 6: 384–390, 2003. doi:10.1038/nn1023.

1012. Tooze SA. Biogenesis of secretory granules in the trans-Golgi network of neuroendocrine and endocrine cells. *Biochim Biophys Acta* 1404: 231–244, 1998. doi:10.1016/S0167-4889(98)00059-7.

1013. Tops M, van Peer JM, Korf J, Wijers AA, Tucker DM. Anxiety, cortisol, and attachment predict plasma oxytocin. *Psychophysiology* 44: 444–449, 2007. doi:10.1111/j.1469-8986.2007.00510.x.

1014. Torner L. Actions of prolactin in the brain: from physiological adaptations to stress and neurogenesis to psychopathology. *Front Endocrinol (Lausanne)* 7: 25, 2016. doi:10.3389/fendo.2016.00025.

1015. Torner L, Maloumby R, Nava G, Aranda J, Clapp C, Neumann ID. In vivo release and gene upregulation of brain prolactin in response to physiological stimuli. *Eur J Neurosci* 19: 1601–1608, 2004. doi:10.1111/j.1460-9568.2004.03264.x.

1016. Torner L, Nava G, Dueñas Z, Corbacho A, Mejía S, López F, Cajero M, Martínez de la Escalera G, Clapp C. Changes in the expression of neurohypophyseal prolactins during the estrous cycle and after estrogen treatment. *J Endocrinol* 161: 423–432, 1999. doi:10.1677/joe.0.1610423.

1017. Torner L, Plotsky PM, Neumann ID, de Jong TR. Forced swimming-induced oxytocin release into blood and brain: Effects of adrenalectomy and corticosterone treatment. *Psychoneuroendocrinology* 77: 165–174, 2017. doi:10.1016/j.psyneuen.2016.12.006.

1019. Torner L, Toschi N, Nava G, Clapp C, Neumann ID. Increased hypothalamic expression of prolactin in lactation: involvement in behavioural and neuroendocrine stress responses. *Eur J Neurosci* 15: 1381–1389, 2002. doi:10.1046/j.1460-9568.2002.01965.x.

1020. Torner L, Toschi N, Pohlinger A, Landgraf R, Neumann ID. Anxiolytic and anti-stress effects of brain prolactin: improved efficacy of antisense targeting of the prolactin receptor by molecular modeling. *J Neurosci* 21: 3207–3214, 2001.

1021. Tost H, Kolachana B, Hakimi S, Lemaitre H, Verchinski BA, Mattay VS, Weinberger DR, Meyer-Lindenberg A. A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic-limbic structure and function. *Proc Natl Acad Sci USA* 107: 13936–13941, 2010. doi:10.1073/pnas.1003296107.

1022. Toth I, Neumann ID. Animal models of social avoidance and social fear. *Cell Tissue Res* 354: 107–118, 2013. doi:10.1007/s00441-013-1636-4.

1023. Toth I, Neumann ID, Slattery DA. Central administration of oxytocin receptor ligands affects cued fear extinction in rats and mice in a timepoint-dependent manner. *Psychopharmacology (Berl)* 223: 149–158, 2012. doi:10.1007/s00213-012-2702-4.

1024. Toth I, Neumann ID, Slattery DA. Social fear conditioning: a novel and specific animal model to study social anxiety disorder. *Neuropsychopharmacology* 37: 1433–1443, 2012. doi:10.1038/npp.2011.329.

1025. Trainor BC, Takahashi EY, Silva AL, Crean KK, Hostetler C. Sex differences in hormonal responses to social conflict in the monogamous California mouse. *Horm Behav* 58: 506–512, 2010. doi:10.1016/j.yhbeh.2010.04.008.

1026. Trencia A, Perfetti A, Cassese A, Vigliotta G, Miele C, Oriente F, Santopietro S, Giacco F, Condorelli G, Formisano P, Beguinot F. Protein kinase B/Akt binds and phosphorylates PED/PEA-15, stabilizing its antiapoptotic action. *Mol Cell Biol* 23: 4511–4521, 2003. doi:10.1128/MCB.23.13.4511-4521.2003.

1027. Tribollet E, Audigier S, Dubois-Dauphin M, Dreifuss JJ. Gonadal steroids regulate oxytocin receptors but not vasopressin receptors in the brain of male and female rats. An autoradiographical study. *Brain Res* 511: 129–140, 1990. doi:10.1016/0006-8993(90)90232-Z.

1028. Tribollet E, Barberis C, Jard S, Dubois-Dauphin M, Dreifuss JJ. Localization and pharmacological characterization of high affinity binding sites for vasopressin and oxytocin in the rat brain by light microscopic autoradiography. *Brain Res* 442: 105–118, 1988. doi:10.1016/0006-8993(88)91437-0.

1029. Tribollet E, Charpak S, Schmidt A, Dubois-Dauphin M, Dreifuss JJ. Appearance and transient expression of oxytocin receptors in fetal, infant, and peripubertal rat brain studied by autoradiography and electrophysiology. *J Neurosci* 9: 1764–1773, 1989.

1030. Tribollet E, Dubois-Dauphin M, Dreifuss JJ, Barberis C, Jard S. Oxytocin receptors in the central nervous system. Distribution, development, and species differences. *Ann N Y Acad Sci* 652: 29–38, 1992. doi:10.1111/j.1749-6632.1992.tb34343.x.

1031. Tribollet E, Li Z, Inenaga K, Yamashita H, Raggenbass M, Dubois-Dauphin M, Dreifuss JJ. Functional neuronal binding sites for oxytocin in the ventromedial hypothalamus of the guinea pig after gonadectomy. *Brain Res* 588: 346–350, 1992. doi:10.1016/0006-8993(92)91598-9.

1032. Tsuda MC, Yamaguchi N, Ogawa S. Early life stress disrupts peripubertal development of aggression in male mice. *Neuroreport* 22: 259–263, 2011. doi:10.1097/WNR.0b013e328344495a.

1033. Uckert S, Becker AJ, Ness BO, Stief CG, Scheller F, Knapp WH, Jonas U. Oxytocin plasma levels in the systemic and cavernous blood of healthy males during different penile conditions. *World J Urol* 20: 323–326, 2003.

1034. Ueda T, Yokoyama Y, Irahara M, Aono T. Influence of psychological stress on suckling-induced pulsatile oxytocin release. *Obstet Gynecol* 84: 259–262, 1994.

1035. Ueta Y, Kannan H, Higuchi T, Negoro H, Yamashita H. CCK-8 excites oxytocin-secreting neurons in the paraventricular nucleus in rats—possible involvement of noradrenergic pathway. *Brain Res Bull* 32: 453–459, 1993. doi:10.1016/0361-9230(93)90290-R.

1036. Uhl-Bronner S, Waltisperger E, Martínez-Lorenzana G, Condes Lara M, Freund-Mercier MJ. Sexually dimorphic expression of oxytocin binding sites in forebrain and spinal cord of the rat. *Neuroscience* 135: 147–154, 2005. doi:10.1016/j.neuroscience.2005.05.025.

1037. Ulloa A, Gonzales AL, Zhong M, Kim YS, Cantlon J, Clay C, Ku CY, Earley S, Sanborn BM. Reduction in TRPC4 expression specifically attenuates G-protein coupled receptor-stimulated increases in intracellular calcium in human myometrial cells. *Cell Calcium* 46: 73–84, 2009. doi:10.1016/j.ceca.2009.05.003.

1038. Unkelbach C, Guastella AJ, Forgas JP. Oxytocin selectively facilitates recognition of positive sex and relationship words. *Psychol Sci* 19: 1092–1094, 2008. doi:10.1111/j.1467-9280.2008.02206.x.

1039. Uvnäs-Moberg K, Arn I, Theorell T, Jonsson CO. Gastrin, somatostatin and oxytocin levels in patients with functional disorders of the gastrointestinal tract and their response to feeding and interaction. *J Psychosom Res* 35: 525–533, 1991. doi:10.1016/0022-3999(91)90047-R.

1040. Vaccari C, Lolait SJ, Ostrowski NL. Comparative distribution of vasopressin V1b and oxytocin receptor messenger ribonucleic acids in brain. *Endocrinology* 139: 5015–5033, 1998. doi:10.1210/endo.139.12.6382.

1041. Valassi E, Scacchi M, Cavagnini F. Neuroendocrine control of food intake. *Nutr Metab Cardiovasc Dis* 18: 158–168, 2008. doi:10.1016/j.numecd.2007.06.004.

1042. van de Bospoort R, Farina M, Schmitz SK, de Jong A, de Wit H, Verhage M, Toonen RF. Munc13 controls the location and efficiency of dense-core vesicle release in neurons. *J Cell Biol* 199: 883–891, 2012. doi:10.1083/jcb.201208024.

1043. van den Burg EH, Neumann ID. Bridging the gap between GPCR activation and behaviour: oxytocin and prolactin signalling in the hypothalamus. *J Mol Neurosci* 43: 200–208, 2011. doi:10.1007/s12031-010-9452-8.

1044. van den Burg EH, Stindl J, Grund T, Neumann ID, Strauss O. Oxytocin stimulates extracellular Ca influx through TRPV2 channels in hypothalamic neurons to exert its

anxiolytic effects. *Neuropsychopharmacology* 40: 2938–2947, 2015. doi:10.1038/npp.2015.147.

1045. Van Kesteren RE, Smit AB, De Lange RP, Kits KS, Van Golen FA, Van Der Schors RC, De With ND, Burke JF, Geraerts WP. Structural and functional evolution of the vasopressin/oxytocin superfamily: vasopressin-related conopressin is the only member present in Lymnaea, and is involved in the control of sexual behavior. *J Neurosci* 15: 5989–5998, 1995.

1046. van Leengoed E, Kerker E, Swanson HH. Inhibition of post-partum maternal behaviour in the rat by injecting an oxytocin antagonist into the cerebral ventricles. *J Endocrinol* 112: 275–282, 1987. doi:10.1677/joe.0.1120275.

1047. van Londen L, Goekoop JG, van Kempen GM, Frankhuijzen-Sierevogel AC, Wiegant VM, van der Velde EA, De Wied D. Plasma levels of arginine vasopressin elevated in patients with major depression. *Neuropsychopharmacology* 17: 284–292, 1997. doi:10.1016/S0893-133X(97)00054-7.

1048. van Roekel E, Verhagen M, Scholte RH, Kleinjan M, Goossens L, Engels RC. The oxytocin receptor gene (OXTR) in relation to state levels of loneliness in adolescence: evidence for micro-level gene-environment interactions. *PLoS One* 8: e77689, 2013. doi:10.1371/journal.pone.0077689.

1049. Van Tol HH, Bolwerk EL, Liu B, Burbach JP. Oxytocin and vasopressin gene expression in the hypothalamo-neurohypophyseal system of the rat during the estrous cycle, pregnancy, and lactation. *Endocrinology* 122: 945–951, 1988. doi:10.1210/endo-122-3-945.

1050. Van Tol HH, Voorhuis DT, Burbach JP. Oxytocin gene expression in discrete hypothalamic magnocellular cell groups is stimulated by prolonged salt loading. *Endocrinology* 120: 71–76, 1987. doi:10.1210/endo-120-1-71.

1051. van Wimersma TB, Dogterom J, de Wied D. Intraventricular administration of antivasopressin serum inhibits. *Life Sci* 16: 637–643, 1975.

1052. Vanderwolf CH, Cain DP. The behavioral neurobiology of learning and memory: a conceptual reorientation. *Brain Res Brain Res Rev* 19: 264–297, 1994. doi:10.1016/0165-0173(94)90015-9.

1053. Vargas-Pinilla P, Paixão-Côrtes VR, Paré P, Tovo-Rodrigues L, Vieira CM, Xavier A, Comas D, Pissinatti A, Sinigaglia M, Rigo MM, Vieira GF, Lucion AB, Salzano FM, Bortolini MC. Evolutionary pattern in the OXT-OXTR system in primates: coevolution and positive selection footprints. *Proc Natl Acad Sci USA* 112: 88–93, 2015. doi:10.1073/pnas.1419399112.

1054. Veenema AH, Beiderbeck DI, Lukas M, Neumann ID. Distinct correlations of vasopressin release within the lateral septum and the bed nucleus of the stria terminalis with the display of intermale aggression. *Horm Behav* 58: 273–281, 2010. doi:10.1016/j.yhbeh.2010.03.006.

1055. Veenema AH, Blume A, Niederle D, Buwalda B, Neumann ID. Effects of early life stress on adult male aggression and hypothalamic vasopressin and serotonin. *Eur J Neurosci* 24: 1711–1720, 2006. doi:10.1111/j.1460-9568.2006.05045.x.

1056. Veenema AH, Bredewold R, Neumann ID. Opposite effects of maternal separation on intermale and maternal aggression in C57BL/6 mice: link to hypothalamic vasopressin and oxytocin immunoreactivity. *Psychoneuroendocrinology* 32: 437–450, 2007. doi:10.1016/j.psyneuen.2007.02.008.

1057. Veening JG, Coolen LM, Gerrits PO. Neural mechanisms of female sexual behavior in the rat; comparison with male ejaculatory control. *Pharmacol Biochem Behav* 121: 16–30, 2014. doi:10.1016/j.pbb.2013.11.025.

1058. Veening JG, de Jong TR, Waldinger MD, Korte SM, Olivier B. The role of oxytocin in male and female reproductive behavior. *Eur J Pharmacol* 753: 209–228, 2015. doi:10.1016/j.ejphar.2014.07.045.

1059. Velmurugan S, Russell JA, Leng G. Systemic leptin increases the electrical activity of supraoptic nucleus oxytocin neurones in virgin and late pregnant rats. *J Neuroendocrinol* 25: 383–390, 2013. doi:10.1111/jne.12016.

1060. Venkatachalam K, Zheng F, Gill DL. Regulation of canonical transient receptor potential (TRPC) channel function by diacylglycerol and protein kinase C. *J Biol Chem* 278: 29031–29040, 2003. doi:10.1074/jbc.M302751200.

1061. Verbalis JG, Mangione MP, Stricker EM. Oxytocin produces natriuresis in rats at physiological plasma concentrations. *Endocrinology* 128: 1317–1322, 1991. doi:10.1210/endo-128-3-1317.

1062. Verbalis JG, Stricker EM, Robinson AG, Hoffman GE. Cholecystokinin activates C-fos expression in hypothalamic oxytocin and corticotropin-releasing hormone neurons. *J Neuroendocrinol* 3: 205–213, 1991. doi:10.1111/j.1365-2826.1991.tb00264.x.

1063. Verhallen RJ, Bosten JM, Goodbourn PT, Lawrance-Owen AJ, Bargary G, Mollon JD. The oxytocin receptor gene (OXTR) and face recognition. *Psychol Sci* 28: 47–55, 2017. doi:10.1177/0956797616672269.

1064. Veronesi MC, Tosi U, Villani M, Govoni N, Faustini M, Kindahl H, Madej A, Carluccio A. Oxytocin, vasopressin, prostaglandin F(2alpha), luteinizing hormone, testosterone, estrone sulfate, and cortisol plasma concentrations after sexual stimulation in stallions. *Theriogenology* 73: 460–467, 2010. doi:10.1016/j.theriogenology.2009.09.028.

1065. Vieira AV, Lamaze C, Schmid SL. Control of EGF receptor signaling by clathrin-mediated endocytosis. *Science* 274: 2086–2089, 1996. doi:10.1126/science.274.5295.2086.

1066. Viero C, Shibuya I, Kitamura N, Verkhratsky A, Fujihara H, Katoh A, Ueta Y, Zingg HH, Chvatal A, Sykova E, Dayanithi G. REVIEW: Oxytocin: Crossing the bridge between basic science and pharmacotherapy. *CNS Neurosci Ther* 16: e138–e156, 2010. doi:10.1111/j.1755-5949.2010.00185.x.

1067. Viviani D, Charlet A, van den Burg E, Robinet C, Hurni N, Abatis M, Magara F, Stoop R. Oxytocin selectively gates fear responses through distinct outputs from the central amygdala. *Science* 333: 104–107, 2011. doi:10.1126/science.1201043.

1068. Viviani D, Terrettaz T, Magara F, Stoop R. Oxytocin enhances the inhibitory effects of diazepam in the rat central medial amygdala. *Neuropharmacology* 58: 62–68, 2010. doi:10.1016/j.neuropharm.2009.06.039.

1069. Wakerley JB, Lincoln DW. The milk-ejection reflex of the rat: a 20- to 40-fold acceleration in the firing of paraventricular neurones during oxytocin release. *J Endocrinol* 57: 477–493, 1973. doi:10.1677/joe.0.0570477.

1070. Walch-Solimena C, Takei K, Marek KL, Midyett K, Südhof TC, De Camilli P, Jahn R. Synaptotagmin: a membrane constituent of neuropeptide-containing large dense-core vesicles. *J Neurosci* 13: 3895–3903, 1993.

1071. Waldherr M, Neumann ID. Centrally released oxytocin mediates mating-induced anxiolysis in male rats. *Proc Natl Acad Sci USA* 104: 16681–16684, 2007. doi:10.1073/pnas.0705860104.

1072. Waldherr M, Nyuyki K, Maloumby R, Bosch OJ, Neumann ID. Attenuation of the neuronal stress responsiveness and corticotrophin releasing hormone synthesis after sexual activity in male rats. *Horm Behav* 57: 222–229, 2010. doi:10.1016/j.yhbeh.2009.11.006.

1073. Walker CD, Toufexis DJ, Burlet A. Hypothalamic and limbic expression of CRF and vasopressin during lactation: implications for the control of ACTH secretion and stress hyporesponsiveness. *Prog Brain Res* 133: 99–110, 2001. doi:10.1016/S0079-6123(01)33008-X.

1074. Waller R, Corral-Frías NS, Vannucci B, Bogdan R, Knodt AR, Hariri AR, Hyde LW. An oxytocin receptor polymorphism predicts amygdala reactivity and antisocial behavior in men. *Soc Cogn Affect Neurosci* 11: 1218–1226, 2016. doi:10.1093/scan/nsw042.

1075. Walum H, Waldman ID, Young LJ. Statistical and methodological considerations for the interpretation of intranasal oxytocin studies. *Biol Psychiatry* 79: 251–257, 2016. doi:10.1016/j.biopsych.2015.06.016.

1076. Wang H, Li S, Kirouac GJ. Role of the orexin (hypocretin) system in contextual fear conditioning in rats. *Behav Brain Res* 316: 47–53, 2017. doi:10.1016/j.bbr.2016.08.052.

1077. Wang SS, Kamphuis W, Huitinga I, Zhou JN, Swaab DF. Gene expression analysis in the human hypothalamus in depression by laser microdissection and real-time PCR: the presence of multiple receptor imbalances. *Mol Psychiatry* 13: 786–799, 2008. doi:10.1038/mp.2008.38.

1078. Wang YF, Hatton GI. Interaction of extracellular signal-regulated protein kinase 1/2 with actin cytoskeleton in supraoptic oxytocin neurons and astrocytes: role in burst firing. *J Neurosci* 27: 13822–13834, 2007. doi:10.1523/JNEUROSCI.4119-07.2007.

1079. Wang Z, Moody K, Newman JD, Insel TR. Vasopressin and oxytocin immunoreactive neurons and fibers in the forebrain of male and female common marmosets

(*Callithrix jacchus*). *Synapse* 27: 14–25, 1997. doi:10.1002/(SICI)1098-2396(199709)27:1<14::AID-SYN2>3.0.CO;2-G.

1080. Watson SJ, Akil H. alpha-MSH in rat brain: occurrence within and outside of beta-endorphin neurons. *Brain Res* 182: 217–223, 1980. doi:10.1016/0006-8993(80)90849-5.

1081. Wei D, Lee D, Cox CD, Karsten CA, Peñagarikano O, Geschwind DH, Gall CM, Piomelli D. Endocannabinoid signaling mediates oxytocin-driven social reward. *Proc Natl Acad Sci USA* 112: 14084–14089, 2015. doi:10.1073/pnas.1509795112.

1082. Weigand A, Feeser M, Gärtner M, Brandt E, Fan Y, Fuge P, Böker H, Bajbouj M, Grimm S. Effects of intranasal oxytocin prior to encoding and retrieval on recognition memory. *Psychopharmacology (Berl)* 227: 321–329, 2013. doi:10.1007/s00213-012-2962-z.

1083. Weisman O, Zagoory-Sharon O, Schneiderman I, Gordon I, Feldman R. Plasma oxytocin distributions in a large cohort of women and men and their gender-specific associations with anxiety. *Psychoneuroendocrinology* 38: 694–701, 2013. doi:10.1016/j.psyneuen.2012.08.011.

1084. Welch MG, Anwar M, Chang CY, Gross KJ, Ruggiero DA, Tamir H, Gershon MD. Combined administration of secretin and oxytocin inhibits chronic colitis and associated activation of forebrain neurons. *Neurogastroenterol Motil* 22: 654–e202, 2010. doi:10.1111/j.1365-2982.2010.01477.x.

1085. Welch MG, Margolis KG, Li Z, Gershon MD. Oxytocin regulates gastrointestinal motility, inflammation, macromolecular permeability, and mucosal maintenance in mice. *Am J Physiol Gastrointest Liver Physiol* 307: G848–G862, 2014. doi:10.1152/ajpgi.00176.2014.

1086. Wiegand V, Gimpl G. Specification of the cholesterol interaction with the oxytocin receptor using a chimeric receptor approach. *Eur J Pharmacol* 676: 12–19, 2012. doi:10.1016/j.ejphar.2011.11.041.

1087. Wigger A, Neumann ID. Endogenous opioid regulation of stress-induced oxytocin release within the hypothalamic paraventricular nucleus is reversed in late pregnancy: a microdialysis study. *Neuroscience* 112: 121–129, 2002. doi:10.1016/S0306-4522(02)00068-4.

1088. Wigger A, Neumann ID. Periodic maternal deprivation induces gender-dependent alterations in behavioral and neuroendocrine responses to emotional stress in adult rats. *Physiol Behav* 66: 293–302, 1999. doi:10.1016/S0031-9384(98)00300-X.

1089. Wigger A, Sánchez MM, Mathys KC, Ebner K, Frank E, Liu D, Kresse A, Neumann ID, Holsboer F, Plotsky PM, Landgraf R. Alterations in central neuropeptide expression, release, and receptor binding in rats bred for high anxiety: critical role of vasopressin. *Neuropsychopharmacology* 29: 1–14, 2004. doi:10.1038/sj.npp.1300290.

1090. Wilhelmi AE, Pickford GE, Sawyer WH. Initiation of the spawning reflex response in Fundulus by the administration of fish and mammalian neurohypophysial preparations and synthetic oxytocin. *Endocrinology* 57: 243–252, 1955. doi:10.1210/endo-57-2-243.

1091. Williams PD, Anderson PS, Ball RG, Bock MG, Carroll L, Chiu SH, Clineschmidt BV, Culberson JC, Erb JM, Evans BE, et al. 1-((7,7-Dimethyl-2(S)-(2(S)-amino-4-(methylsulfonyl)butyramido)bicyclo [2.2.1]-heptan-1(S)-yl)methyl)sulfonyl)-4-(2-methylphenyl)piperaz ine (L-368,899): an orally bioavailable, non-peptide oxytocin antagonist with potential utility for managing preterm labor. *J Med Chem* 37: 565–571, 1994. doi:10.1021/jm00031a004.

1092. Williams PD, Clineschmidt BV, Erb JM, Freidinger RM, Guidotti MT, Lis EV, Pawluczyk JM, Pettibone DJ, Reiss DR, Veber DF, et al. 1-(1-[4-[(N-acetyl-4-piperidinyl)oxy]-2-methoxybenzoyl]piperidin-4-yl)-4H–3,1-benzoxazin-2(1H)-one (L-371,257): a new, orally bioavailable, non-peptide oxytocin antagonist. *J Med Chem* 38: 4634–4636, 1995. doi:10.1021/jm00023a002.

1093. Williams TD, Carter DA, Lightman SL. Sexual dimorphism in the posterior pituitary response to stress in the rat. *Endocrinology* 116: 738–740, 1985. doi:10.1210/endo-116-2-738.

1094. Windle RJ, Kershaw YM, Shanks N, Wood SA, Lightman SL, Ingram CD. Oxytocin attenuates stress-induced c-fos mRNA expression in specific forebrain regions associated with modulation of hypothalamo-pituitary-adrenal activity. *J Neurosci* 24: 2974–2982, 2004. doi:10.1523/JNEUROSCI.3432-03.2004.

1095. Windle RJ, Shanks N, Lightman SL, Ingram CD. Central oxytocin administration reduces stress-induced corticosterone release and anxiety behavior in rats. *Endocrinology* 138: 2829–2834, 1997. doi:10.1210/endo.138.7.5255.

1096. Winslow JT, Hastings N, Carter CS, Harbaugh CR, Insel TR. A role for central vasopressin in pair bonding in monogamous prairie voles. *Nature* 365: 545–548, 1993. doi:10.1038/365545a0.

1097. Winslow JT, Hearn EF, Ferguson J, Young LJ, Matzuk MM, Insel TR. Infant vocalization, adult aggression, and fear behavior of an oxytocin null mutant mouse. *Horm Behav* 37: 145–155, 2000. doi:10.1006/hbeh.1999.1566.

1098. Winslow JT, Insel TR. Social status in pairs of male squirrel monkeys determines the behavioral response to central oxytocin administration. *J Neurosci* 11: 2032–2038, 1991.

1099. Witt DM, Carter CS, Walton DM. Central and peripheral effects of oxytocin administration in prairie voles (*Microtus ochrogaster*). *Pharmacol Biochem Behav* 37: 63–69, 1990. doi:10.1016/0091-3057(90)90042-G.

1100. Wotjak CT, Ganster J, Kohl G, Holsboer F, Landgraf R, Engelmann M. Dissociated central and peripheral release of vasopressin, but not oxytocin, in response to repeated swim stress: new insights into the secretory capacities of peptidergic neurons. *Neuroscience* 85: 1209–1222, 1998. doi:10.1016/S0306-4522(97)00683-0.

1101. Wotjak CT, Kubota M, Liebsch G, Montkowski A, Holsboer F, Neumann I, Landgraf R. Release of vasopressin within the rat paraventricular nucleus in response to emotional stress: a novel mechanism of regulating adrenocorticotropic hormone secretion? *J Neurosci* 16: 7725–7732, 1996.

1102. Wotjak CT, Naruo T, Muraoka S, Simchen R, Landgraf R, Engelmann M. Forced swimming stimulates the expression of vasopressin and oxytocin in magnocellular neurons of the rat hypothalamic paraventricular nucleus. *Eur J Neurosci* 13: 2273–2281, 2001. doi:10.1046/j.0953-816x.2001.01613.x.

1103. Wouters E, Hudson CA, McArdle CA, Bernal AL. Central role for protein kinase C in oxytocin and epidermal growth factor stimulated cyclooxygenase 2 expression in human myometrial cells. *BMC Res Notes* 7: 357, 2014. doi:10.1186/1756-0500-7-357.

1104. Wrzal PK, Devost D, Pétrin D, Goupil E, Iorio-Morin C, Laporte SA, Zingg HH, Hébert TE. Allosteric interactions between the oxytocin receptor and the β2-adrenergic receptor in the modulation of ERK1/2 activation are mediated by heterodimerization. *Cell Signal* 24: 342–350, 2012. doi:10.1016/j.cellsig.2011.09.020.

1105. Wrzal PK, Goupil E, Laporte SA, Hébert TE, Zingg HH. Functional interactions between the oxytocin receptor and the β2-adrenergic receptor: implications for ERK1/2 activation in human myometrial cells. *Cell Signal* 24: 333–341, 2012. doi:10.1016/j.cellsig.2011.09.019.

1106. Wu GY, Deisseroth K, Tsien RW. Activity-dependent CREB phosphorylation: convergence of a fast, sensitive calmodulin kinase pathway and a slow, less sensitive mitogen-activated protein kinase pathway. *Proc Natl Acad Sci USA* 98: 2808–2813, 2001. doi:10.1073/pnas.051634198.

1107. Xiao L, Priest MF, Nasenbeny J, Lu T, Kozorovitskiy Y. Biased oxytocinergic modulation of midbrain dopamine systems. *Neuron* 95: 368–384.e5, 2017. doi:10.1016/j.neuron.2017.06.003.

1108. Xu C, You X, Liu W, Sun Q, Ding X, Huang Y, Ni X. Prostaglandin F2α regulates the expression of uterine activation proteins via multiple signalling pathways. *Reproduction* 149: 139–146, 2015. doi:10.1530/REP-14-0479.

1109. Yaghmaie P, Koudelka CW, Simpson EL. Mental health comorbidity in patients with atopic dermatitis. *J Allergy Clin Immunol* 131: 428–433, 2013. doi:10.1016/j.jaci.2012.10.041.

1110. Yamada M, Hirao K, Namiki C, Hanakawa T, Fukuyama H, Hayashi T, Murai T. Social cognition and frontal lobe pathology in schizophrenia: a voxel-based morphometric study. *Neuroimage* 35: 292–298, 2007. doi:10.1016/j.neuroimage.2006.10.046.

1111. Yamashita K, Kitano T. Molecular evolution of the oxytocin-oxytocin receptor system in eutherians. *Mol Phylogenet Evol* 67: 520–528, 2013. doi:10.1016/j.ympev.2013.02.017.

1112. Yang SP, Voogt JL. Mating-activated nitric oxide-producing neurons in specific brain regions in the female rat. *Brain Res* 950: 79–87, 2002. doi:10.1016/S0006-8993(02)03004-4.

1113. Yi KJ, So KH, Hata Y, Suzuki Y, Kato D, Watanabe K, Aso H, Kasahara Y, Nishimori K, Chen C, Katoh K, Roh SG. The regulation of oxytocin receptor gene expression during adipogenesis. *J Neuroendocrinol* 27: 335–342, 2015. doi:10.1111/jne.12268.

1114. Ying L, Becard M, Lyell D, Han X, Shortliffe L, Husted CI, Alvira CM, Cornfield DN. The transient receptor potential vanilloid 4 channel modulates uterine tone during pregnancy. *Sci Transl Med* 7: 319ra204, 2015. doi:10.1126/scitranslmed.aad0376.

1115. Yoon YJ, Wu B, Buxbaum AR, Das S, Tsai A, English BP, Grimm JB, Lavis LD, Singer RH. Glutamate-induced RNA localization and translation in neurons. *Proc Natl Acad Sci USA* 113: E6877–E6886, 2016. doi:10.1073/pnas.1614267113.

1116. Yoshida M, Takayanagi Y, Inoue K, Kimura T, Young LJ, Onaka T, Nishimori K. Evidence that oxytocin exerts anxiolytic effects via oxytocin receptor expressed in serotonergic neurons in mice. *J Neurosci* 29: 2259–2271, 2009. doi:10.1523/JNEUROSCI.5593-08.2009.

1117. Yoshimura R, Kiyama H, Kimura T, Araki T, Maeno H, Tanizawa O, Tohyama M. Localization of oxytocin receptor messenger ribonucleic acid in the rat brain. *Endocrinology* 133: 1239–1246, 1993. doi:10.1210/endo.133.3.8396014.

1118. Young KA, Liu Y, Gobrogge KL, Wang H, Wang Z. Oxytocin reverses amphetamine-induced deficits in social bonding: evidence for an interaction with nucleus accumbens dopamine. *J Neurosci* 34: 8499–8506, 2014. doi:10.1523/JNEUROSCI.4275-13.2014.

1119. Young LJ, Huot B, Nilsen R, Wang Z, Insel TR. Species differences in central oxytocin receptor gene expression: comparative analysis of promoter sequences. *J Neuroendocrinol* 8: 777–783, 1996. doi:10.1046/j.1365-2826.1996.05188.x.

1120. Young LJ, Muns S, Wang Z, Insel TR. Changes in oxytocin receptor mRNA in rat brain during pregnancy and the effects of estrogen and interleukin-6. *J Neuroendocrinol* 9: 859–865, 1997. doi:10.1046/j.1365-2826.1997.00654.x.

1121. Young LJ, Wang Z. The neurobiology of pair bonding. *Nat Neurosci* 7: 1048–1054, 2004. doi:10.1038/nn1327.

1122. Young LJ, Wang Z, Donaldson R, Rissman EF. Estrogen receptor alpha is essential for induction of oxytocin receptor by estrogen. *Neuroreport* 9: 933–936, 1998. doi:10.1097/00001756-199803300-00031.

1123. Young WS III, Shepard E, Amico J, Hennighausen L, Wagner KU, LaMarca ME, McKinney C, Ginns EI. Deficiency in mouse oxytocin prevents milk ejection, but not fertility or parturition. *J Neuroendocrinol* 8: 847–853, 1996. doi:10.1046/j.1365-2826.1996.05266.x.

1124. Younger J, Aron A, Parke S, Chatterjee N, Mackey S. Viewing pictures of a romantic partner reduces experimental pain: involvement of neural reward systems. *PLoS One* 5: e13309, 2010. doi:10.1371/journal.pone.0013309.

1125. Yuan L, Liu S, Bai X, Gao Y, Liu G, Wang X, Liu D, Li T, Hao A, Wang Z. Oxytocin inhibits lipopolysaccharide-induced inflammation in microglial cells and attenuates microglial activation in lipopolysaccharide-treated mice. *J Neuroinflammation* 13: 77, 2016. doi:10.1186/s12974-016-0541-7.

1126. Yuen KW, Garner JP, Carson DS, Keller J, Lembke A, Hyde SA, Kenna HA, Tennakoon L, Schatzberg AF, Parker KJ. Plasma oxytocin concentrations are lower in depressed vs. healthy control women and are independent of cortisol. *J Psychiatr Res* 51: 30–36, 2014. doi:10.1016/j.jpsychires.2013.12.012.

1127. Yulia A, Singh N, Lei K, Sooranna SR, Johnson MR. Cyclic AMP effectors regulate myometrial oxytocin receptor expression. *Endocrinology* 157: 4411–4422, 2016. doi:10.1210/en.2016-1514.

1128. Zaninetti M, Raggenbass M. Oxytocin receptor agonists enhance inhibitory synaptic transmission in the rat hippocampus by activating interneurons in stratum pyramidale. *Eur J Neurosci* 12: 3975–3984, 2000. doi:10.1046/j.1460-9568.2000.00290.x.

1129. Zatkova M, Reichova A, Bacova Z, Strbak V, Kiss A, Bakos J. Neurite outgrowth stimulated by oxytocin is modulated by inhibition of the calcium voltage-gated channels. *Cell Mol Neurobiol* 38: 371–378, 2018. doi:10.1007/s10571-017-0503-3.

1130. Zetzsche T, Frasch A, Jirikowski G, Murck H, Steiger A. Nocturnal oxytocin secretion is reduced in major depression. *Biol Psychiatry* 39: 584, 1996. doi:10.1016/0006-3223(96)84235-1.

1131. Zhang CL, McKinsey TA, Lu JR, Olson EN. Association of COOH-terminal-binding protein (CtBP) and MEF2-interacting transcription repressor (MITR) contributes to transcriptional repression of the MEF2 transcription factor. *J Biol Chem* 276: 35–39, 2001. doi:10.1074/jbc.M007364200.

1132. Zhang F, Wang LP, Brauner M, Liewald JF, Kay K, Watzke N, Wood PG, Bamberg E, Nagel G, Gottschalk A, Deisseroth K. Multimodal fast optical interrogation of neural circuitry. *Nature* 446: 633–639, 2007. doi:10.1038/nature05744.

1133. Zhang G, Cai D. Circadian intervention of obesity development via resting-stage feeding manipulation or oxytocin treatment. *Am J Physiol Endocrinol Metab* 301: E1004–E1012, 2011. doi:10.1152/ajpendo.00196.2011.

1134. Zhang G, Zhang Y, Fast DM, Lin Z, Steenwyk R. Ultra sensitive quantitation of endogenous oxytocin in rat and human plasma using a two-dimensional liquid chromatography-tandem mass spectrometry assay. *Anal Biochem* 416: 45–52, 2011. doi:10.1016/j.ab.2011.04.041.

1135. Zhang XH, Filippi S, Vignozzi L, Morelli A, Mancina R, Luconi M, Donati S, Marini M, Vannelli GB, Forti G, Maggi M. Identification, localization and functional in vitro and in vivo activity of oxytocin receptor in the rat penis. *J Endocrinol* 184: 567–576, 2005. doi:10.1677/joe.1.05885.

1136. Zhang Y, Gray TS, D'Souza DN, Carrasco GA, Damjanoska KJ, Dudas B, Garcia F, Zainelli GM, Sullivan Hanley NR, Battaglia G, Muma NA, Van de Kar LD. Desensitization of 5–HT1A receptors by 5–HT2A receptors in neuroendocrine neurons in vivo. *J Pharmacol Exp Ther* 310: 59–66, 2004. doi:10.1124/jpet.103.062224.

1137. Zhang Z, Bhalla A, Dean C, Chapman ER, Jackson MB. Synaptotagmin IV: a multifunctional regulator of peptidergic nerve terminals. *Nat Neurosci* 12: 163–171, 2009. doi:10.1038/nn.2252.

1138. Zhao M, New L, Kravchenko VV, Kato Y, Gram H, di Padova F, Olson EN, Ulevitch RJ, Han J. Regulation of the MEF2 family of transcription factors by p38. *Mol Cell Biol* 19: 21–30, 1999. doi:10.1128/MCB.19.1.21.

1139. Zheng R, Studzinski GP. Optimal AraC-cytotoxicity to AML cells requires ERK5 activity. *J Cell Biochem* 118: 1583–1589, 2017. doi:10.1002/jcb.25820.

1140. Zhong M, Boseman ML, Millena AC, Khan SA. Oxytocin induces the migration of prostate cancer cells: involvement of the Gi-coupled signaling pathway. *Mol Cancer Res* 8: 1164–1172, 2010. doi:10.1158/1541-7786.MCR-09-0329.

1141. Zhong M, Murtazina DA, Phillips J, Ku CY, Sanborn BM. Multiple signals regulate phospholipase CBeta3 in human myometrial cells. *Biol Reprod* 78: 1007–1017, 2008. doi:10.1095/biolreprod.107.064485.

1142. Zhong M, Yang M, Sanborn BM. Extracellular signal-regulated kinase 1/2 activation by myometrial oxytocin receptor involves Galpha(q)Gbetagamma and epidermal growth factor receptor tyrosine kinase activation. *Endocrinology* 144: 2947–2956, 2003. doi:10.1210/en.2002-221039.

1143. Zhou XB, Lutz S, Steffens F, Korth M, Wieland T. Oxytocin receptors differentially signal via Gq and Gi proteins in pregnant and nonpregnant rat uterine myocytes: implications for myometrial contractility. *Mol Endocrinol* 21: 740–752, 2007. doi:10.1210/me.2006-0220.

1144. Zhu L, Onaka T. Involvement of medullary A2 noradrenergic neurons in the activation of oxytocin neurons after conditioned fear stimuli. *Eur J Neurosci* 16: 2186–2198, 2002. doi:10.1046/j.1460-9568.2002.02285.x.

1145. Ziegler C, Dannlowski U, Bräuer D, Stevens S, Laeger I, Wittmann H, Kugel H, Dobel C, Hurlemann R, Reif A, Lesch KP, Heindel W, Kirschbaum C, Arolt V, Gerlach AL, Hoyer J, Deckert J, Zwanzger P, Domschke K. Oxytocin receptor gene methylation: converging multilevel evidence for a role in social anxiety. *Neuropsychopharmacology* 40: 1528–1538, 2015. doi:10.1038/npp.2015.2.

1146. Zimmermann-Peruzatto JM, Lazzari VM, Agnes G, Becker RO, de Moura AC, Guedes RP, Lucion AB, Almeida S, Giovenardi M. The impact of oxytocin gene knockout on sexual behavior and gene expression related to neuroendocrine systems in the brain of female mice. *Cell Mol Neurobiol* 37: 803–815, 2017. doi:10.1007/s10571-016-0419-3.

1147. Zingg HH, Lefebvre DL. Oxytocin and vasopressin gene expression during gestation and lactation. *Brain Res* 464: 1–6, 1988.

1148. Zoicas I, Slattery DA, Neumann ID. Brain oxytocin in social fear conditioning and its extinction: involvement of the lateral septum. *Neuropsychopharmacology* 39: 3027–3035, 2014. doi:10.1038/npp.2014.156.