



Review

Oxytocin, vasopressin, and social recognition in mammals

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Abstract

While pheromones may act as social memory signals, oxytocin and vasopressin acting in the brain appear to be critical for the neural processing of olfactory signatures used for social discrimination. Evidence from a variety of laboratories using a range of animal models, as well as an array of molecular and pharmacological techniques, have helped to determine the neuroanatomical and functional roles oxytocin and vasopressin play in social cognition. In this review we discuss the considerable evidence for the roles of oxytocin and vasopressin in social recognition in rats and mice, as well as in offspring recognition in sheep and mate preference in monogamous voles.

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1. Introduction

The ability to recognize a familiar conspecific is the foundation for all mammalian social relationships, including parent-offspring recognition, mate recognition, and dominant-subordinate hierarchies. All of these behavioral processes require social discrimination which is a specific type of memory that differs from other types of learning and memory and may be subserved by distinct anatomical and neurochemical circuits in the brain. While humans and non-human primates rely primarily on visual and auditory cues for individual recognition, many other mammals rely on olfactory or pheromonal cues to differentiate individuals. The neural processing of these olfactory cues is critical to social memory and is dependent on the integrity of the neuropeptide systems for oxytocin (OT) and vasopressin (AVP). While many peptides may serve as important pheromonal cues in mammalian and non-mammalian species, OT and AVP are critical to the mammalian ability to process such cues in an appropriate manner.

OT and AVP are closely related nonapeptides. They are transcribed from adjacent genes and differ by only two amino acids, suggesting that they arose from an ancestral gene by gene duplication. They are produced in discrete regions of the brain and are released both centrally into the brain, and peripherally into the circulation. OT and AVP destined for peripheral release is made in the magnocellular neurons of the paraventricular nucleus (PVN) and supra-optic nucleus (SON) of the hypothalamus and released into the bloodstream by the posterior pituitary. Peripherally, OT acts in the uterus to facilitate parturition and in the breast to facilitate milk ejection during lactation. AVP, also known as anti-diuretic hormone (ADH), acts in the kidney to facilitate re-absorption of water and the blood vessels to regulate vascular tone [28]. Centrally, these peptides are produced in the parvocellular cells of the PVN as well as in extra-hypothalamic sites [11]. Receptors for these peptides are found in a variety of specific regions of the brain suggesting that they may play many different roles centrally.

The majority of evidence for OT and AVP as social memory peptides comes from the considerable investigations in the rat and mouse. The role of these neuropeptides in more complex forms of social memory, particularly in parent-offspring bonds in sheep and pair bonding in voles has also

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been well established. Through the use of pharmacological agents, transgenics, and viral vectors the specific roles and brain regions involved in peptide mediated social cognition is being elucidated. OT and AVP have been shown to be critical in the olfactory processing of social cues at many levels of the olfactory circuit and throughout the brain. Furthermore, OT and AVP mediated social memory can be quite potent lasting from 1 hour in rodents to a lifetime in voles. This review will cover the evidence for OT and AVP in rodent social recognition as well as offspring recognition in sheep and mate preference in pair bonding voles.

2. Social recognition in rodents

Social recognition tests are a group of learning and memory tasks that were originally created as a non-aversive alternative to the avoidance paradigms that had been traditionally used to examine learning and memory behaviors [57]. While social recognition is a model of learning and memory, these tests have more recently illustrated the unique aspects of social cognition. Social recognition tests make use of the animals' natural tendency towards olfactory investigation of novel conspecifics. Anogenital and head sniffing, as well as close following, are considered olfactory investigation. While there are now a wide variety of social recognition paradigms, they tend to follow one of either two basic models. In the habituation–dishabituation paradigm, the test animal is repeatedly exposed to a stimulus animal, either a juvenile male or ovariectomized female. Repeated presentations lead to a marked decrease in the amount of time the test animal spends in olfactory investigation of the stimulus animal. At the end, the test animal is exposed to a novel stimulus animal and, normally, the time spent in investigation returns to the original level (Fig. 1A). This controls for the possibility of fatigue or disinterest [26]. In the social discrimination paradigm, the test animal is exposed to the stimulus animal and then, after a certain interval, simultaneously presented with the same stimulus and a novel stimulus. Normally the test animal will spend significantly more time investigating the novel stimulus animal as compared to the original stimulus animal (Fig. 1B) [21]. In both paradigms, the time in between trials can be varied to test for facilitation or impairment of social recognition. While, originally, social recognition was introduced as a non-aversive paradigm for testing the effects of AVP on learning and memory in general; it is now well established that social recognition is a unique form of learning and memory utilizing distinct neural mechanisms specific for social processing, and is a critical component of the social brain.

2.1. Vasopressin

The ability of AVP to modulate complex behavior was originally observed in the 1960s by David de Wied, and focused on the ability of AVP to potentiate avoidance learning

and memory [22,61]. Furthermore, the learning and memory deficits in the naturally occurring AVP mutant Brattleboro rat supported these findings [59]. These early studies lead to the hypothesis of a greater role for AVP in many types of learning and memory.

The early investigations of AVP and social recognition focused on the ability of subcutaneously administered AVP to facilitate social recognition in male rats by prolonging the duration during which the memory is held [10]. Conversely, male Brattleboro rats which lack AVP were found to have impaired social recognition. This impairment could be rescued by microdialysis administration of AVP into the septum [19], providing strong evidence for a physiological role of AVP in social recognition.

Since these early studies there have been many published reports on the effects of AVP agonist and antagonist administration on social recognition in rats. Intracerebro-ventricular (icv) injections of AVP into male rats immediately after the initial encounter with a stimulus animal resulted in a similar potentiation of social memory, as did peripheral AVP administration [40]. Electrical and osmotic stimulation of the SON and PVN in male rats resulted in a release of AVP in the hypothalamus and a facilitation of social recognition [20]. Peripheral AVP antagonist injections impaired social recognition in intact male rats, but had no effect on castrated ones [6,10] suggesting a role for sex hormones in the control of social recognition. Central administration of anti-AVP serum also resulted in impaired social recognition in male rats [60].

While peripheral and central injections of AVP agonists and antagonists clearly demonstrate a role for AVP in social recognition, studies using site-specific injections of these agents help clarify the significance of certain brain regions in AVP-mediated social recognition. The lateral septum contains a dense plexus of AVP projections from the medial amygdala (MeA) and bed nucleus of the stria terminalis (BNST) as well as a high density of AVP receptors, making it a natural target for study [7,11,13,31,54,55]. Site-specific injections of AVP into the lateral septum of male rats resulted in a facilitation of social recognition by prolonging the time over which the memory was held, as did septal AVP administration using retrodialysis [19,23]. Furthermore, osmotic stimulation of the SON and PVN in male rats resulted in an increase in intra-hypothalamic and intra-septal AVP and improved social recognition [20]. Conversely, lateral septum administration of a non-selective AVP antagonist blocked normal social recognition in male rats [23,24]. Social recognition was also disrupted by administration of anti-AVP serum into the ventral and dorsal hippocampus and the dorsal lateral septum [60].

Using pharmacology, the principle role of AVP has been well established but the existence of two central brain receptors for AVP, namely V1a receptor (V1aR) and V1b receptor (V1bR), has made it difficult to determine which AVP receptor is involved in social recognition. Both receptors are seven transmembrane, G-protein coupled receptors of the Gq/11 class, differing in their binding affinities for different ligands [66]. Historically, the V1bR was thought to exist only in the

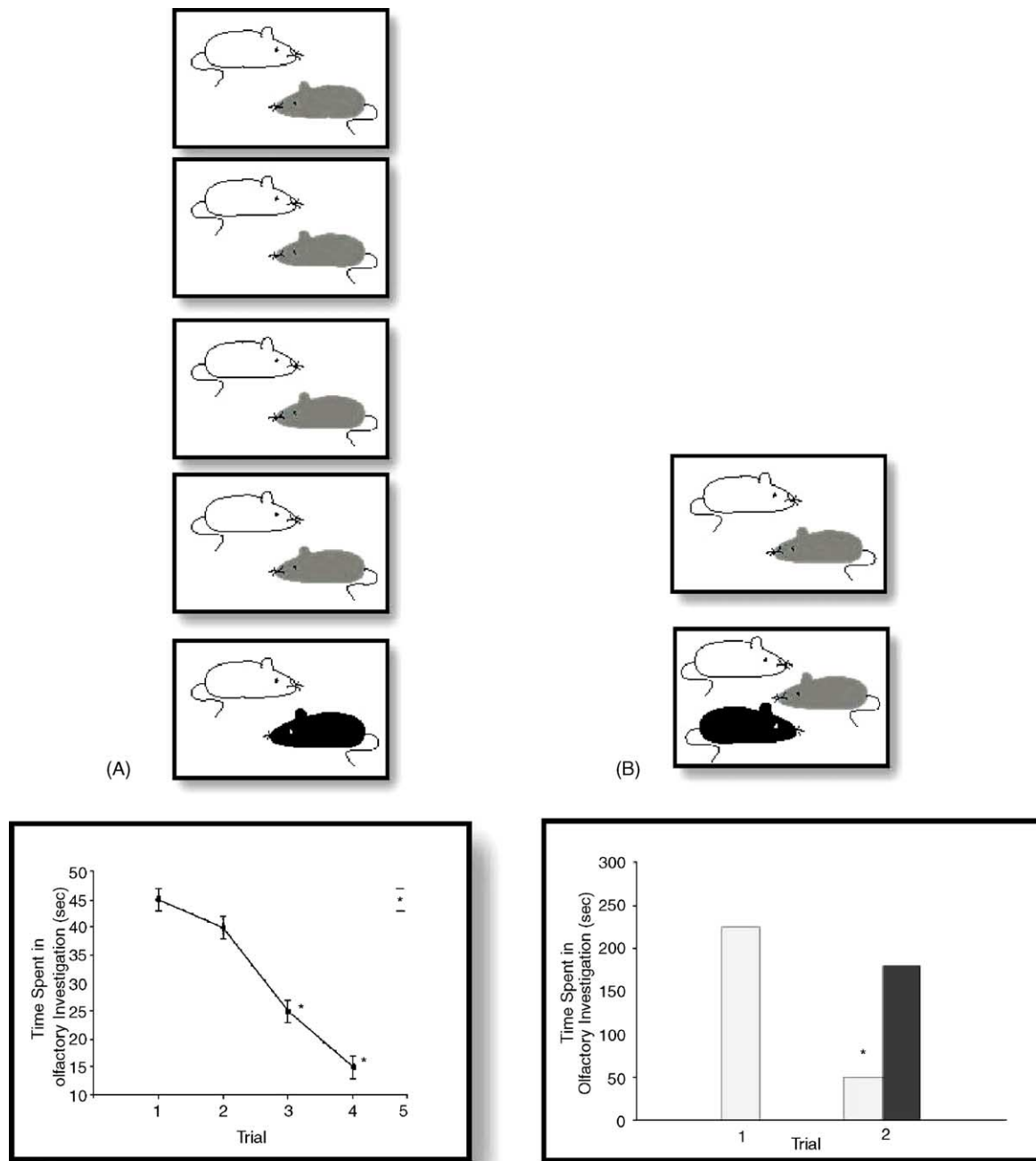


Fig. 1. Social recognition paradigms for rodents. (A) Social habituation–dishabituation paradigm. The test animal is exposed to the same stimulus animal for four successive one minute trials with a set inter-trial interval. During the fifth dishabituation trial the test animal is exposed to a novel stimulus animal. (B) Social discrimination paradigm. During the first trial, the test animal is exposed to a stimulus animal for five minutes. During the second trial, after a set inter-trial interval, the test animal is exposed to the same stimulus animal and a novel stimulus animal. Data shown are idealized data typically obtained in these paradigms.

anterior pituitary, while the V1aR is located in many areas throughout the brain. However, recent evidence suggests that the V1bR is also located in several discrete regions throughout the brain [1,58]. Both receptor subtypes could mediate AVP effects on social recognition; however most of the behavioral effects of AVP have been attributed to the V1aR.

The use of selective V1aR antagonists suggests this subtype to be critical in social recognition. Icv administration of

a V1aR antagonist blocks social recognition in male rats, as does V1aR antagonist administered by retrodialysis into the lateral septum [19,39]. Furthermore, V1aR antagonists block the potentiation of social recognition caused by increased AVP release in response to osmotic stimulation [20].

The importance of the V1aR in social recognition has also been demonstrated using a variety of molecular techniques. Antisense oligodeoxynucleotides to the V1aR mRNA were

created in order to develop and test a knockdown strategy for investigating the importance of this receptor in behavior. The antisense oligos were infused into the lateral septum of male rats by osmotic minipumps. This resulted in a significant decrease in V1aR density in the lateral septum as measured by receptor autoradiography. The decrease in V1aR levels resulted in a complete disruption of social recognition [39].

Conversely, the same group used viral vectors to over express the V1aR. An adeno-associated viral vector containing the prairie vole V1aR was bilaterally infused into the lateral septum of normal rats. This resulted in a stable increase in V1aR binding of 344%. The over expression of V1aR in the lateral septum resulted in a facilitation of social recognition by prolonging the time over which the memory is held; the ability to recognize a familiar conspecific was extended beyond controls, and was nearly significant at 24 h. This facilitation was blocked by microdialysis administration of a selective V1aR antagonist [38].

A critical role for the V1aR in social recognition has also been demonstrated in male mice. A V1aR knockout mouse (V1aRKO) was created that completely lacks functional V1aR. These mice show no V1aR binding in the brain and show a complete disruption in social recognition (Fig. 2A and B). This deficit is not due to a general deficit in olfaction. When the social recognition paradigm was repeated with a scented cotton ball, scented with either coconut, or anise extract, instead of stimulus animals, the V1aRKO animals were able to habituate and dishabituate to this non-social scent (Fig. 2C). This suggests that the actions of V1aR and AVP in social recognition are specific for social odors and not in detection and/or processing of all scents. These mice also performed normally in non-social learning and memory tasks, such as the Morris Water Maze, as well as tests for sensorimotor gating, such as pre-pulse inhibition [4].

While the V1aR has been shown to be critical in social recognition, there is mounting evidence for a role of the V1bR as well. Male V1bR knockout mice (V1bRKO) that lack a functional V1bR have also been shown to have a mild deficit in social recognition in the two tests for social memory. In the habituation paradigm the V1bRKO were slower to recognize the stimulus animal but did “catch-up” to the WT and recognized the stimulus animal eventually. In the discrimination test the V1bRKO did demonstrate a significant deficit in social recognition. This social recognition deficit appears less profound than the V1aRKO mice suggesting that the V1bR receptor may play a less significant role in short-term social recognition. Female V1bRKO mice did differ significantly in the Bruce effect, a more long-term test of social memory. The Bruce effect is a phenomenon in which a previously mated female will block the implantation of fertilized eggs if exposed to an unfamiliar male after the initial mating. This effect requires a more long-term social memory of the olfactory signature of the original male and the ability to recognize the novel male as unfamiliar. Female V1bRKO mice did not display the Bruce effect and remained pregnant regardless of the exposure to a novel male [56].

AVP's critical role in social recognition has been known since the 1980s and with the development of better pharmacological agents and newer molecular technologies including transgenic mice and viral vectors, the exact role of AVP and its receptors in rodent social recognition has become clearer. It is evident that this neuropeptide plays a fundamental part in the animal's ability to process the olfactory and pheromonal cues of conspecifics.

2.2. *Oxytocin*

The historical evidence for the role of OT in social recognition is less straightforward and complete as compared to AVP; however, it is clear from more recent investigations that OT is critical for normal social recognition in both male and female rats and mice.

It was originally suggested that OT and AVP had opposing effects on memory, with AVP facilitating, and OT attenuating learning and memory. The initial studies on OT in social memory showed an attenuation of social recognition when OT was administered peripherally in high doses in male rats [49]. This attenuation was blocked with administration of OT antagonists. The resulting plasma levels of OT were subsequently found to be well outside the physiological levels for this peptide [49]. Later studies with more physiological levels of OT demonstrated that peripheral administration of OT at low doses, in fact, facilitated social recognition in male rats [51]. These findings suggest that the effects of OT on social recognition follow an inverted U-shaped dose response curve where moderate doses facilitate, and high doses attenuate social recognition. The same dose response curve has been found in OT administered centrally (icv) in male rats. OT antagonist administered centrally blocked the facilitating effects of low dose OT but did not disrupt social recognition per se. This antagonist also blocked the attenuation effects of high doses of OT [2]. It has been demonstrated that different regions of the OT molecule are responsible for the facilitation and attenuation effects of OT on social recognition, suggesting that OT may facilitate and attenuate social memory using distinctive mechanisms [50]. Icv administration of OT in female rats did not facilitate social memory, but administration of OT antagonists did interfere with the animals' ability to establish normal social memory [18]. The ability of OT agonists to facilitate social recognition in males and not female and the ability of OT antagonists to interfere with normal social recognition in females but not males suggested the possibility of a sexual dimorphism with respect to the roles of OT in social recognition in the rat.

The evidence for OT in social recognition in mice, both female and male, is more straight-forward than that in rats. Investigations of an OT knockout (OTKO) mouse revealed a total deficit in social recognition. Male OTKO mice, which completely lack the OT peptide, never displayed the typical reduction in olfactory investigation upon repeated exposures to the same stimulus female. Like the V1aRKO mice, this deficit was not due to a more general deficit in olfaction as

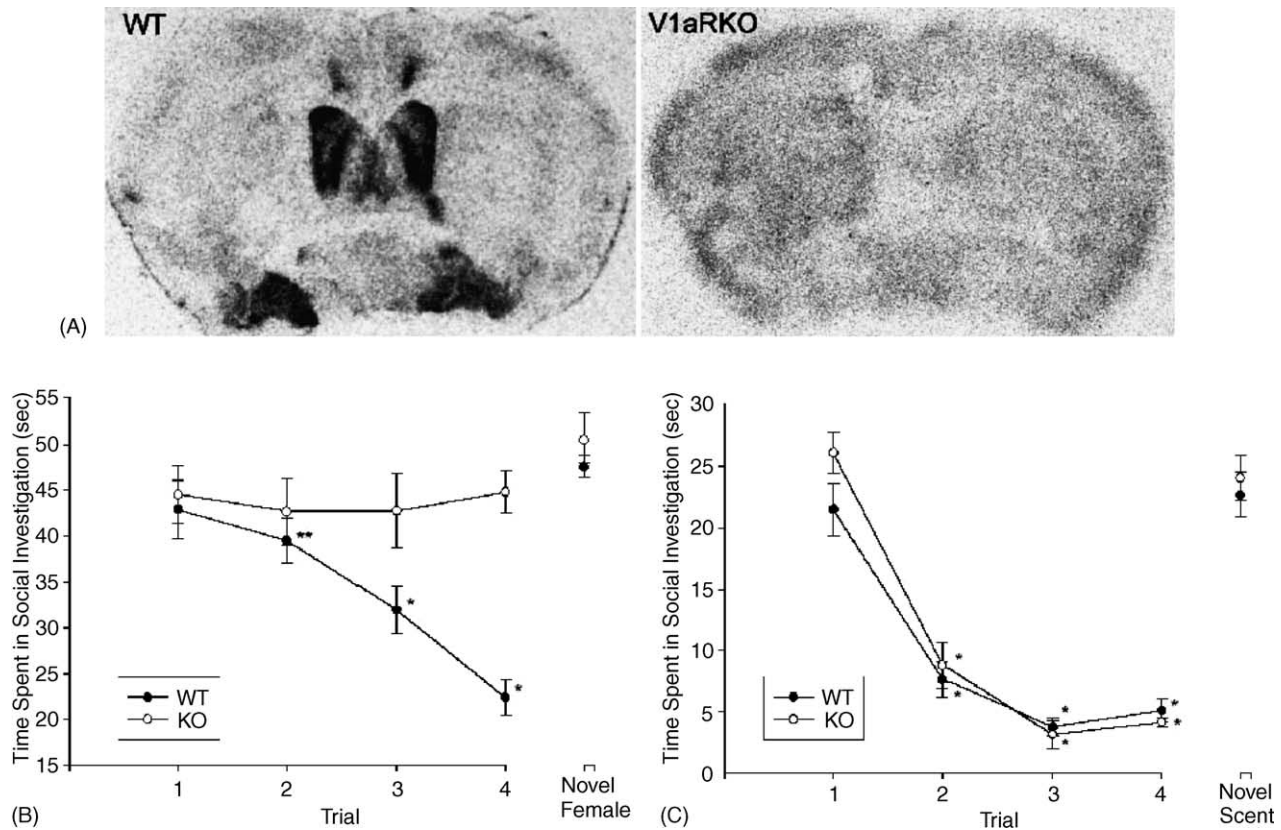


Fig. 2. V1aRKO, social recognition and olfactory habituation. (A) V1aR binding autoradiograms illustrating ^{125}I linear V1aR antagonist binding in WT and V1aRKO males at the level of the lateral septum. (B) Social recognition of V1aRKO (open circles) and WT (closed circles) was measured as a difference in olfactory investigation of the same ovariectomized female during each of four successive 1 minute trials (ITI = 10 min). A fifth dishabituation trial depicts the response to a novel female in a one-minute pairing 10 min after the fourth trial. WT mice showed a significant decrease in olfactory investigation after repeated pairings of the same female on trials 3 and 4. V1aRKO mice never showed a decrease in olfactory investigation. (C) Olfactory habituation was measured as a difference in olfactory investigation of an anise scented cotton ball during each of four successive 1 minutes trial (ITI = 10 min). The fifth, dishabituation trial depicts the response to a coconut scented cotton ball in a one minute exposure 10 min after the fourth trial. Both WT (closed circles) and V1aRKO (open circles) mice showed a decrease in investigation upon subsequent presentations of the same scented cotton ball on trials 2, 3, and 4. $**P < 0.01$, $*P < 0.001$. Error bars represent \pm S.E.M. Asterisks represent a significant decrease between each trial as compared to the first trial. Reprinted from [4].

they were able to habituate to a scented cotton ball used as a non-social olfactory stimulus, suggesting that OT is critical to the processing of specifically social cues. These animals showed normal OT receptor distribution and quantity using autoradiography, as well as, normal non-social learning and memory as measured by the Morris Water Maze [26,47]. The deficit in social recognition was reversible with both icv and site-specific injections of OT. Furthermore, normal social recognition was blocked in the WT mice with a single icv injection of OT antagonist before the initial encounter [25]. The ability to rescue social recognition in OTKO mice with a single injection of OT clearly demonstrates the importance of this peptide in the processing of social cues and subsequent social recognition in the male mouse.

The social recognition deficits of the OTKO mice are not limited to male mice. The female OTKO mice also show a significant deficit in social recognition that was not attributable to other behavioral changes. In addition, OTKO females are unable to distinguish healthy from parasite infected males during mate selection [8,32]. The essential role of OT in social memory in female mice has also been demonstrated by

the effects of OTKO on the Bruce effect. OTKO females failed to remain pregnant if re-exposed to either their mate or a novel male. Only females that were allowed to remain with their mate maintained pregnancy [56]. This inability to distinguish between the mate and novel male in the OTKO females demonstrates the importance of OT in long-term social memory as well as short-term social recognition.

2.3. Anatomical and neurochemical circuitry of social recognition

As important as the neuropeptides, are the anatomical regions in which they act and the other systems with which they interact. The behavioral effects of site-specific agonists and antagonists demonstrate not only a dependence of social memory on OT and AVP, but also a critical involvement of certain brain regions for the effects of these neuropeptides. It is evident that OT and AVP do not act alone to mediate social recognition, but must interact with, and possibly modulate, other neurotransmitter systems. Finally, the time of action of these neuropeptides also appears to be critical to their effects

on social memory. Because of the complex nature of social behavior, the effects of these neuropeptides cannot be fully understood without a discussion of anatomy, neurochemistry, and timing.

Evidence suggests that both OT and AVP act in specific brain regions and that some of these regions are common while others appear specific for the different neuropeptides. Furthermore the anatomical regions involved in rodent social recognition are, not surprisingly, those that mediate olfaction, learning and memory, and those areas that express receptors for the neuropeptides.

Social recognition in rats and mice begins with the detection of pheromones from the conspecific. One class of individual recognition signals and pheromones are thought to be in the animals' urine and in mice small volatile pheromones that are bound and released by the major urinary proteins (MUPs). MUPs are highly polymorphic and the patterns of MUPs may confer the unique olfactory signatures that are critical to individual recognition in mice, as well as effecting delivery of pheromones to the chemosensory receptor neurons in the olfactory epithelium and vomeronasal organ [3,44]. The vomeronasal organ projects to the accessory olfactory bulb (AOB), and the olfactory epithelium projects to the main olfactory bulb (MOB). The AOB and MOB project to higher brain regions that have been shown to be involved in OT and AVP mediated social recognition, including the MeA and the lateral septum [17,42,53]. It is possible therefore that the pheromones produced by the conspecific are initially delivered to the olfactory systems via MUPs and that these signals are modulated in the bulbs and in higher brain regions by OT and AVP in order to generate social memory. Clearly, MUPs are not the only signal produced by a conspecific that can serve as an olfactory signature. Another example is female hamster vaginal secretions which contain pheromones and could help confer individual specificity in hamsters [52].

In addition to their roles in pheromonal detection, the olfactory bulbs and the vomeronasal organ have also been demonstrated as regions critical to OT and AVP effects on social recognition. Bilateral injections of either AVP or OT into the olfactory bulbs of male rats resulted in a facilitation of social recognition; however, antagonists to AVP and OT did not have an effect on normal social recognition [15]. This raises the possibility that the actions of OT and AVP in the olfactory bulbs are pharmacological and not physiological effects. However, rats that have had the vomeronasal organ removed show a decrease in social investigation, temporarily impaired social recognition, and were no longer responsive to an AVP antagonist [5].

In the olfactory system, OT and AVP have been shown to directly interact with other neurotransmitter systems. Of these systems, the NE system appears to be critical to AVP and OT-mediated social memory. Depletion of NE using 6-OHDA in the olfactory bulbs of male rats abolishes AVP and OT facilitation of social recognition but does not block normal social recognition [16]. In OT-mediated facilitation of social recognition, it has been shown that retrodialysis of

OT into the olfactory bulb of male rats increases NE release and that this activates α -adrenoreceptors. This activation is necessary for OT facilitation in the olfactory bulb [14]. These data suggest that AVP and OT may affect social recognition by activating the NE system.

To determine what higher order anatomical regions are involved in OT-mediated social recognition, c-fos immunocytochemistry was used in the OTKO mice. After a brief social encounter with a stimulus animal, male WT animals showed Fos-immunoreactivity (IR) in the MeA, the BNST, the medial preoptic area (MPOA), the MOB and the AOB, the lateral septum, the cortical amygdala, and the piriform cortex. The OTKO mice showed Fos-IR in all of these areas except, the MeA, the BNST, and the MPOA. Given that the MeA receives olfactory input from the AOB and the MOB, and that the BNST and the MPOA are down stream from the MeA, the MeA was chosen as the target for site-specific injections. OT injections into the MeA in the OTKO rescued social recognition and OT antagonist injected into the MeA in WT blocked normal social recognition [25]. These findings suggest that the MeA is critical for OT-mediated social recognition. Furthermore, lesion studies of the amygdala have shown this area to be critically involved in a variety of social behaviors [9,48].

As discussed above, the lateral septum appears to be a critical brain region for the effects of AVP on social recognition. The lateral septum is involved in a wide variety of behavioral processes that are related to higher order cognitive function. It has an extensive network of reciprocal inter-connections with many higher order brain regions involved in social behaviors and learning and memory, including the MeA, hippocampus, and hypothalamus [7,11,12,27,54]. Furthermore, the lateral septum receives AVP projections from the MeA and BNST and contains a high density of AVP receptors [11,13,54]. The site-specific studies mentioned previously clearly implicate the lateral septum as a critical region in the AVP effect on rodent social recognition.

The hippocampus has also been shown to be important in social recognition. Ibotenic lesions of the hippocampus disrupts normal social recognition in mice [37]. In rats, surgical lesions of the hippocampus and related structures also impaired social recognition and behavior [45,46]. Anti-AVP serum injected into the dorsal or ventral hippocampus impairs social recognition and anti-OT serum injected into the ventral but not the dorsal hippocampus also impairs social recognition in male rats [60]. Given its role in learning and memory and its afferent connections from the lateral septum [7,54], it is not surprising that the hippocampus is involved in social memory and that this may be modulated by neuropeptides.

The ability of rats and mice to form social memories of a conspecific is clearly complex as it involves a number of diverse brain regions and other neurochemical systems, however, the complexity does not end there. The timing of AVP and OT activity also appears to be important to their ability to influence social recognition. As mentioned previously, OT administration rescued social recognition in the OTKO only if given before the initial encounter with the conspecifics

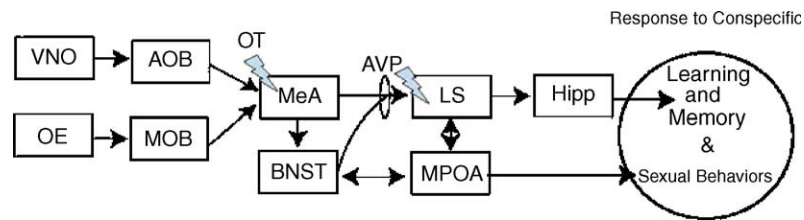


Fig. 3. Social recognition and olfactory pathways in rats and mice. Schematic depicts the hypothetical pathways from olfactory activation to higher cognitive processing as deduced from studies in rats and mice. Abbreviations: AOB, accessory olfactory bulb; AVP, vasopressin; BNST, bed nucleus of the stria terminalis; Hipp, hippocampus; LS, lateral septum; MeA, medial amygdala; MOB, main olfactory bulb; MPOA, medial preoptic area; OE, olfactory epithelium; OT, oxytocin; VNO, vomeronasal organ. Some connections are not shown for simplicity.

[25]. To be effective, AVP can be administered either before, or after the initial encounter [15,40]. This suggests that these two closely related neuropeptides may play different parts in the generation and facilitation of social memory. OT may be critical in the initial processing or encoding of social cues, whereas AVP may be critical for the retention and recall of such cues [25].

While all of the brain structures and neurochemicals discussed above are involved in social recognition, it is still unclear how they work together to affect complex social memory. The anatomy and circuitry of these regions do, however, allow for the development of a unifying theory on how the diverse anatomical regions work in concert with OT, AVP, and other neurochemicals to elicit social recognition. The initial detection of the conspecific's pheromones and individual identification via MUPS is detected in the vomeronasal organ and the olfactory epithelium which project to the AOB and MOB respectively [5,17,42,53]. The olfactory bulbs project to the MeA where OT acts to modulate the initial social encounter and formation of social memory. The MeA projects to the BNST and both of these regions send AVP projections to the lateral septum where AVP acts to modulate the processing and/or recall of social cues. The lateral septum is reciprocally connected to the hippocampus which is critical for the storage and retrieval of many types of memories. The lateral septum is also connected to the MPOA in the hypothalamus which is critical for sexual behaviors. NE may act at many of these areas to affect social recognition (Fig. 3). The proposed circuit is hypothetical and has been deduced from the studies discussed above; clearly there may be species differences in the anatomical connections and the sites of action of neuropeptides and neuromodulators.

3. Social recognition in complex social behaviors

Historically, social recognition has been studied in rats and mice and has been defined as the ability to recognize a familiar conspecific over a relatively short period of time. While OT and AVP can increase the duration of social recognition, this type of social memory is still considered short-term. There are other examples of social recognition in other species that are more enduring and can be considered permanent social memories. OT and AVP are critical in these diverse and more

complex long-term social memories as well. Two excellent examples of these stable and long-lasting social memories can be seen in the ability of a ewe to recognize and bond with its offspring and the ability of a prairie voles to establish a selective and enduring pair-bond with its mate. In both of these examples OT and/or AVP plays a critical role.

3.1. Offspring recognition in sheep

Sheep are seasonal breeders who live in large social groups; therefore, many young are born around the same time [33]. It is critical to their reproductive success that the mother ewe is able to immediately recognize and bond with her offspring. This strong selective bond is formed within 1–2 h after birth and an enduring social memory is required for this bond [33].

Maternal behavior in sheep, unlike rodents, cannot be induced with only gonadal hormone administration. Steroid hormonally primed sheep require vaginocervical stimulation in order to induce maternal behavior and more importantly to trigger the formation of the olfactory memory necessary to recognize the offspring. C-fos and lesions studies have identified several brain regions to be important in offspring recognition and maternal behavior in ewes. Some of these brain regions are the same as those critical in social recognition in rats and mice. These regions include the MeA, lateral septum, MPOA, BNST, olfactory bulbs and hippocampus, and all of these regions contain OT cells, terminals, or fibers [33].

Given this evidence and the findings in rats and mice, it is not surprising that OT plays a critical role in offspring recognition and maternal bonding in sheep. OT release at birth or in response to vaginocervical stimulation has been shown in the BNST, MPOA, and the lateral septum, regions known to be important in social memory in rodents [33]. Icv OT administration can induce a full maternal response in nonparturient, multiparous ewes and cerebrospinal fluid levels of OT are elevated in post-partum ewes [34,36].

OT appears to facilitate offspring recognition and maternal bonding by inhibiting the aversive responses of the ewe to the amniotic fluid odors and by inhibiting the aggressive responses to the lamb. These aversive behaviors are thought to be mediated by projections from the olfactory bulbs through the amygdala and BNST to the MPOA. OT could act on these projections at multiple points to inhibit this aversion and facil-

itate the offspring recognition that is critical to the induction and survival of the maternal bond [33].

The most direct role for OT in offspring recognition however, occurs in the olfactory bulbs. The effects of vaginocervical stimulation are dependent on signals sent to the brain via the spinal cord and this signal appears to be NE. The signals from the vaginocervical stimulation cause a release of OT in the olfactory bulbs. This OT appears to mediate the release of γ -aminobutyric acid (GABA), NE and acetylcholine (ACh) in the bulbs [41]. The release of NE and ACh is associated with an increase in the mitral cells that respond to the lamb's odor. The mitral cells receive and transmit olfactory information and are modulated by GABA containing granular cells. The OT associated increase in GABA release from granular cells may help modulate the response of mitral cells to the lamb's odor and may result in a change in firing frequency, or tuning, of these neurons that codes for the specific odor of the offspring lamb [35]. While many neurotransmitters are involved in selective offspring recognition in ewes, OT appears to be the common signal for the release of these neurotransmitters and the resulting development of the selective olfactory memory and inhibition of the natural aversion to amniotic fluid [41].

3.2. *Pair-bonding in the Prairie vole*

Another example of OT and AVP in long-term social memory is the complex social behavior of the monogamous prairie vole. Prairie voles are a mouse-like rodent native to North America. These animals, both female and male, form a lasting pair bond with their mate and are biparental. This is in contrast to the closely related montane vole which is promiscuous and uniparental [64]. Given the social differences between these related species, they present a unique opportunity to use a comparative approach to study the social bonds which are dependent on accurate social memory.

Similar to the offspring bonding in ewes, OT appears to play a critical role in the social-bonding in female prairie voles and the ability to form a selective pair-bond is dependent on the ability to recognize the mate. OT administration facilitates and OT antagonist prevents the formation of this pair-bond in females [29]. In males, AVP appears to be the critical peptide as agonists facilitate and antagonists prevent bonding [62]. In both males and females mating stimulates the formation of the pair bond [64].

Using the comparative approach mentioned above, it has been determined that the neuroanatomical specificity of receptor expression is responsible for the actions of OT and AVP in the pair-bonding prairie voles. The distribution of the receptors for these neuropeptides differs greatly between the monogamous and promiscuous species. In the prairie voles the OT receptors are located in the nucleus accumbens and the AVP receptors are located in the ventral pallidum. The montane voles do not show this receptor distribution for either peptide [30,65]. The nucleus accumbens and the ventral pallidum are both critical parts of the reward circuitry in the

brain. It has been proposed that the convergent activation of the OT and AVP systems involved in individual recognition and the reward pathways in response to mating may lead to an association between the olfactory signature of the partner and the rewarding nature of sex with that partner. This convergence may then lead to the formation of the conditioned partner preference and the subsequent pair bond [43,63]. The memory of the olfactory signature of the mate would be critical to the activation of the system and the ability to form a selective pair bond, and OT and AVP might play the key role in the formation of this odor memory. Similar to rat and mice social recognition, it is clear that the specific neuroanatomical sites of action of OT and AVP are essential to mate preference in pair-bonding.

4. Conclusions

Social recognition is critical for the formation and maintenance of all social relationships. The social behaviors of mammalian species varies greatly; however, social cognition forms the basis for both simple and complex social behaviors and OT and AVP play a fundamental role in the ability to form and retain these memories. Rats and mice use social recognition to recognize a familiar conspecific. Ewes use social memory to form the critical memory of their offspring; prairie voles use social memory to recognize their mate during pair-bonding. The physiological importance of these peptides in social cognition has been proven through the use of receptor antagonists and knockouts that disrupt the endogenous system and subsequently result in impairments in social behaviors. However, not all regions that show pharmacological responses to exogenous peptide administration are necessarily dependent on endogenous peptide actions under normal conditions. Although both central and peripheral administration of AVP and OT effect social recognition, the findings discussed in this review using site-specific antagonists, antisense injections and localized viral vector expression have shown that the actions of these peptide are localized to distinct regions in the brain. The precise mechanisms by which OT and AVP regulate social recognition are still unclear; however, through the combination of pharmacology, transgenics, and viral vector technology, we are beginning to elucidate the neural mechanisms involved in the processing of pheromonal cues from a conspecific.

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References

- [1] Barberis C, Tribollet E. Vasopressin and oxytocin receptors in the central nervous system. *Crit Rev Neurobiol* 1996;10(1):119–54.

- [2] Benelli A, Bertolini A, Poggioli R, Menozzi B, Basaglia R, Arletti R. Polymodal dose-response curve for oxytocin in the social recognition test. *Neuropeptides* 1995;28:251–5.
- [3] Beynon RJ, Hurst JL. Multiple roles of major urinary proteins in the house mouse, *mus domesticus*. *Biochem Soc Trans* 2003;31(1):142–6.
- [4] Bielsky IF, Bao-Hu S, Szegda KL, Westphal H, Young LJ. Profound impairment in social recognition and reduction in anxiety-like behavior in vasopressin V1a receptor knockout mice. *Neuropsychopharmacology* 2004;29:483–93.
- [5] Bluthé RM, Dantzer R. Role of the vomeronasal system in vasopressinergic modulation of social recognition in rats. *Brain Res* 1993;604(1–2):205–10.
- [6] Bluthé RM, Schoenen J, Dantzer R. Androgen-dependent vasopressinergic neurons are involved in social recognition in rats. *Brain Res* 1990;519:150–7.
- [7] Caffé AR, van Leeuwen FW, Luiten PG. Vasopressin cells in the medial amygdala of the rat project to the lateral septum and ventral hippocampus. *J Comp Neurol* 1987;261(2):237–52.
- [8] Choleris E, Gustafsson J-A, Korach KS, Muglia LJ, Pfaff DW, Ogawa S. An estrogen-dependent four-gene micronet regulating social recognition: a study with oxytocin and estrogen receptor- α and - β knockout mice. *Proc Natl Acad Sci USA* 2003;100(10):6192–7.
- [9] Daenen EWPM, Wolterink G, Gerrits MAFM, van Ree JM. The effects of neonatal lesions in the amygdala or ventral hippocampus on social behaviour later in life. *Behav Brain Res* 2002;136:571–82.
- [10] Dantzer R, Bluthé RM, Koob GF, Le Moal M. Modulation of social memory in male rats by neurohypophyseal peptides. *Psychopharmacology* 1987;91:363–8.
- [11] de Vries GJ, Buijs RM. The origin of vasopressinergic and oxytocinergic innervation of the rat brain with special reference to the lateral septum. *Brain Res* 1983;273:307–17.
- [12] de Vries GJ, Buijs RM, van Leeuwen FW, Caffé AR, Swaab DF. The vasopressinergic innervation of the brain in normal and castrated rats. *J Comp Neurol* 1985;233(2):236–54.
- [13] de Vries GJ, Miller MA. Anatomy and function of extra-hypothalamic vasopressin systems in the brain. *Prog Brain Res* 1998;119:3–20.
- [14] Dluzen DE, Muraoka S, Engelmann M, Ebner K, Landgraf R. Oxytocin induces preservation of social recognition in male rats by activating α -adrenoceptors of the olfactory bulb. *Eur J Neurosci* 2000;12:760–6.
- [15] 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 recognition responses in male rats. *Peptides* 1998;19(6):999–1005.
- [16] Dluzen DE, Muraoka S, Landgraf R. Olfactory bulb norepinephrine depletion abolishes vasopressin and oxytocin preservation of social recognition responses in rats. *Neurosci Lett* 1998;254:161–4.
- [17] Dulac C, Torello AT. Molecular detection of pheromone signals in mammals: from genes to behaviour. *Nat Rev* 2003;4:551–62.
- [18] Engelmann M, Ebner K, Wotjak CT, Landgraf R. Endogenous oxytocin is involved in short-term olfactory memory in female rats. *Behav Brain Res* 1998;90:89–94.
- [19] Engelmann M, Landgraf R. Microdialysis administration of vasopressin into the septum improves social recognition in Brattleboro rats. *Physiol Behav* 1994;55:145–9.
- [20] Engelmann M, Ludwig M, Landgraf R. Simultaneous monitoring of intracerebral release and behavior: vasopressin improves social recognition. *J Neuroendocrinol* 1994;6:391–5.
- [21] Engelmann M, Wotjak CT, Landgraf R. Social discrimination procedure: an alternative method to investigate juvenile recognition abilities in rats. *Physiol Behav* 1995;58:315–21.
- [22] Engelmann M, Wotjak CT, Neumann ID, Ludwig M, Landgraf R. Behavioral consequences of intracerebral vasopressin and oxytocin: focus on learning and memory. *Neurosci Biobehav Rev* 1996;20(3):341–58.
- [23] Everts HGJ, Koolhaas JM. Lateral septum vasopressin in rats: role in social and object recognition? *Brain Res* 1997;760:1–7.
- [24] Everts HGJ, Koolhaas JM. Differential modulation of lateral septal vasopressin receptor blockade in spatial-learning, social recognition, and anxiety-related behaviors in rats. *Behav Brain Res* 1999;99:7–16.
- [25] Ferguson JN, Aldag JM, Insel TR, Young LJ. Oxytocin in the medial amygdala is essential for social recognition in the mouse. *J Neurosci* 2001;21(20):8278–85.
- [26] Ferguson JN, Young LJ, Hearn EF, Matzuk MM, Insel TR, Winslow JT. Social amnesia in mice lacking the oxytocin gene. *Nat Genet* 2000;25:284–8.
- [27] Ferris CF, Gold L, de Vries GJ, Potegal M. Evidence for the function and anatomical relationship between the lateral septum and the hypothalamus in the control of flank marking behavior in Golden hamsters. *J Comp Neurol* 1990;293(3):476–85.
- [28] Gainer H, Wray S. Cellular and molecular biology of oxytocin and vasopressin. New York: Raven Press; 1994.
- [29] Insel TR, Hulihan T. A gender-specific mechanism for pair bonding: oxytocin and partner preference formation in monogamous voles. *Behav Neurosci* 1995;109:782–9.
- [30] Insel TR, Shapiro LE. Oxytocin receptor distribution reflects social organization in monogamous and polygamous voles. *Proc Natl Acad Sci USA* 1992;89:5981–5.
- [31] Johnson AE, Audigier S, Rossi F, Jard S, Tribollet E, Barberis C. Localization and characterization of vasopressin binding sites in the rat brain using an iodinated linear AVP antagonist. *Brain Res* 1993;622(1/2):9–16.
- [32] Kavaliers M, Colwell DD, Choleris E, Agma A, Muglia LJ, Ogawa S, et al. Impaired discrimination of and aversion to parasitized male odors by female oxytocin knockout mice. *Genes Brain Behav* 2003;2(4):220–30.
- [33] Kendrick KM, da Costa APC, Broad KD, Ohkura S, Guevara R, Levy F, et al. Neural control of maternal behavior and olfactory recognition of offspring. *Brain Res Bull* 1997;44(4):383–95.
- [34] Kendrick KM, Keverne EB, Baldwin BA, Sharman DF. Cerebrospinal fluid levels of acetylcholinesterase, monoamines, and oxytocin, during labour, parturition, vaginocervical stimulation, lamb separation, and suckling in sheep. *Neuroendocrinology* 1986;44:149–56.
- [35] Kendrick KM, Levy F, Keverne EB. Changes in the sensory processing of olfactory signals induced by birth in sheep. *Science* 1992;256:833–6.
- [36] Keverne EB, Kendrick KM. Oxytocin facilitation of maternal behavior in sheep. *Ann NY Acad Sci* 1992;652:83–101.
- [37] Kogan JH, Frankland PW, Silva AJ. Long-term memory underlying hippocampus-dependent social recognition in mice. *Hippocampus* 2000;10:47–56.
- [38] Landgraf R, Frank E, Aldag JM, Neumann ID, Ren X, Terwilliger EF, et al. Viral vector-mediated gene transfer of the vole V1a vasopressin receptor in the rat septum: improved social discrimination and active social behavior. *Eur J Neurosci* 2003;18(2):403–11.
- [39] Landgraf R, Gerstberger R, Montkowski A, Probst JC, Wotjak CT, Holsboer F, et al. V1 vasopressin receptor antisense oligodeoxynucleotide into the septum reduced vasopressin binding, social discrimination abilities, and anxiety-related behavior in rats. *J Neurosci* 1995;15:4250–8.
- [40] Le Moal M, Dantzer R, Michaud B, Koob GF. Centrally injected arginine vasopressin (AVP) facilitates social memory in rats. *Neurosci Lett* 1987;77:353–9.
- [41] Levy F, Kendrick KM, Goode JA, Guevara-Guzman R, Keverne EB. Oxytocin and vasopressin release in the olfactory bulb of parturient ewes: changes with maternal experience and effects acetylcholine, g-aminobutyric acid, glutamate and noradrenalin release. *Brain Res* 1995;669:197–206.
- [42] Li CS, Kaba H, Saito H, Seto K. Neural mechanisms underlying the action of primer pheromones in mice. *Neuroscience* 1990;36(3):773–8.

- [43] Lim MM, Young LJ. Vasopressin-dependent neural circuits underlying pair bond formation in the monogamous prairie vole. *Neuroscience*; in press.
- [44] Luo M, Fee MS, Katz LC. Encoding pheromonal signals in the accessory olfactory bulb of behaving mice. *Science* 2003;299:1196–201.
- [45] Maaswinkel H, Baars A-M, Gispen W-H, Spruijt BM. Roles of the basolateral amygdala and hippocampus in social recognition in rats. *Physiol Behav* 1996;60(1):55–63.
- [46] Maaswinkel H, Gispen WH, Spruijt BM. Executive function of the hippocampus in social behavior in the rat. *Behav Neurosci* 1997;111(4):777–84.
- [47] 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* 1996;93:11699–704.
- [48] Oakes ME, Coover GD. Effects of small amygdala lesions on fear, but not aggression, in the rat. *Physiol Behav* 1996;61(1):45–55.
- [49] Popik P, Vetulani J. Opposite actions of oxytocin and its peptide antagonists on social memory in rats. *Neuropeptides* 1991;18:23–7.
- [50] Popik P, Vetulani J, Ree JMV. Facilitation and attenuation of social recognition in rats by different oxytocin-related peptides. *Eur J Pharmacol* 1996;308:113–6.
- [51] Popik P, Vetulani J, van Ree JM. Low doses of oxytocin facilitate social recognition in rats. *Psychopharmacology* 1992;106(71).
- [52] Powers JB, Bergondy ML. Androgenic regulation of chemoinvestigatory behaviors in male and females hamsters. *Horm Behav* 1983;17(1):28–44.
- [53] Scalia F, Winans SS. The differential projections of the olfactory bulb and accessory olfactory bulb in mammals. *J Comp Neurol* 1975;161(1):31–55.
- [54] Sheehan T, Numan M. The septal region and social behavior. New York: Springer; 2000.
- [55] Szot P, Dorsa DM. Differential timing and sexual dimorphism in the expression of the vasopressin gene in the developing rat brain. *Brain Res Dev Brain Res* 1993;73(2):177–83.
- [56] Temple JL, Young WS, III, Wersinger SR. Disruption of the genes for either oxytocin or the vasopressin 1B receptor alters male-induced pregnancy block (the Bruce effect). Abstract in Society for Neuroscience. New Orleans; 2003.
- [57] Thor DH, Holloway WR. Social memory of the male laboratory rat. *J Comp Physiol Psychol* 1982;96:1000–6.
- [58] Vaccari C, Lalait SJ, Ostrowski NL. Comparative distribution of vasopressin V1b and oxytocin receptor messenger ribonucleic acids in brain. *Endocrinology* 1998;139(12):5015–33.
- [59] van Wimersma Greidanus TB. Disturbed behavior and memory of the Brattelboro rat. *Ann NY Acad Sci* 1982;394:655–62.
- [60] van Wimersma Greidanus TB, Maigret C. The role of limbic vasopressin and oxytocin in social recognition. *Brain Res* 1996;713:153–9.
- [61] van Wimersma Greidanus TB, van Ree JM, de Wied D. Vasopressin and memory. *Pharmacol Ther* 1983;20(3):437–58.
- [62] Winslow JT, Hastings N, Carter CS, Harbaugh CR, Insel TR. A role for central vasopressin in pair bonding in monogamous prairie voles. *Nature* 1993;365.
- [63] Young LJ, Lim MM, Gingrich B, Insel TR. Cellular mechanisms of social attachment. *Horm Behav* 2001;40(2):133–8.
- [64] Young LJ, Wang Z, Insel TR. Neuroendocrine bases of monogamy. *Trends Neurosci* 1998;21(2):71–5.
- [65] Young LJ, Winslow JT, Nilsen R, Insel TR. Species differences in V1a receptor gene expression in monogamous and non-monogamous voles: behavioral consequences. *Behav Neurosci* 1997;111(3):599–605.
- [66] Zingg HH. Vasopressin and oxytocin receptors. *Baillieres Clin Endo Metab* 1996;10(1):75–96.