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The Neuroendocrine Basis of Social Recognition

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All social relationships are dependent on an organism's ability to remember conspecifics. Social memory may be a unique form of memory, critical for reproduction, territorial defense, and the establishment of dominance hierarchies in a natural context. In the laboratory, social memory can be assessed reliably by measuring the reduction in investigation of a familiar partner relative to novel conspecifics. The neurohypophyseal neuropeptides oxytocin and vasopressin have been shown to influence a number of forms of social behavior, including affiliation, aggression, and reproduction. This article reviews vasopressin and oxytocin effects on social cognition, particularly the acquisition and retention of social recognition in rats and mice. Studies in rats have demonstrated that vasopressin in specific neural pathways, such as the lateral septum, is necessary for social recognition. As vasopressin facilitates recall when given after an initial encounter, the peptide appears important for the consolidation not the acquisition of a social memory. Although oxytocin has complex effects on social memory in rats, mice with a null mutation of the oxytocin gene are completely socially amnestic without other cognitive deficits evident. As oxytocin given centrally before but not after the initial encounter restores social recognition in these mutant mice, the neuropeptide appears critical for the acquisition rather than the consolidation phase of memory. Oxytocin's effects on social memory are mediated via a discrete cell population in the medial amygdala. These findings support the hypothesis that vasopressin and oxytocin are essential for social memory, although they appear to influence different cognitive processes and may modulate different neural systems. KEY WORDS: oxytocin; vasopressin; oxytocin receptors; vasopressin receptors; social memory; medial amygdala; olfactory bulb; α-adrenergic receptors.

INTRODUCTION

Across species, the ability to recognize a familiar individual forms the foundation upon which all social relationships are built. In some cases it may be advantageous to remember only very general characteristics about other individuals, such as gender or reproductive state, but in other cases it may be necessary to remember specific details of individual social status or kinship. The ability to encode and recall very specific, individual information of this second type is required of almost all organisms living in complex social systems. In humans and other primates, individual recognition relies mostly on

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visual and auditory cues. Indeed, in the human brain, a specific visual association area, the right fusiform gyrus, appears to be critical for face recognition (69, 91). Patients with lesions of this region have prosopagnosia, the inability to recognize faces, but show few if any other visual or memory deficits (82). In the monkey brain, cells in the temporal cortex appear to respond selectively to faces with responses in certain cells related to familiarity (98, 99). In most other mammals, social information is encoded via olfactory or pheromonal signals, although auditory and visual signals may have important influences (108).

Whatever the sensory source of the information, the consequences of individual recognition are profound for reproduction and species survival. Kin recognition, pair bond formation, selective pregnancy termination, and dominance hierarchies all depend on the long-term capacity of individuals to differentiate among familiar, previously encountered conspecifics. In addition to these forms of long-term social recognition (29, 68, 74), rodents are also known to form transient, short-term memories of recently encountered individuals (117). The behavioral aspects of social recognition and social memory have been reviewed elsewhere (48, 104). In this article, we describe the neuroendocrine basis of these behaviors. Our primary focus is on the neuropeptides vasopressin (AVP) and oxytocin (OT), with a description of recent transgenic studies that have identified specific neural pathways mediating the effects of these neuropeptides on social recognition in rodents. We also describe results with other neuropeptides and neurotransmitters that suggest future directions for this area of research. This article is limited to studies with rodents because of our neuroendocrine focus. A more comprehensive treatment of kin recognition and social cognition can be found elsewhere (5, 55, 100).

SOCIAL MEMORY: PARADIGMS AND PROBLEMS

Based on the natural tendency of rats and mice to intensely investigate novel individuals, Thor and Holloway proposed a simple laboratory test to investigate short-term, social recognition capacities (116). When an unfamiliar conspecific is introduced for the first time into the home cage of an adult male rat or mouse, the resident male vigorously investigates the novel individual. If the novel animal is removed and then reintroduced to the same resident male a short time later, it will receive far less investigation during the second meeting. This effect does not represent habituation or satiation on the part of the resident male since the presentation of a novel animal during the second encounter triggers a bout of intense anogenital investigation indistinguishable from the first. Based on this simple observation, it is possible to use changes in the duration of investigation during repeated pairings with the same stimulus animal as an index of memory for that individual (Fig. 1a). This is a short-term memory. In male rats, if the interval between the exposures to the same individual exceeds 30–60 min, there will be no decline in the duration of investigation during the second encounter, indicating that the resident male

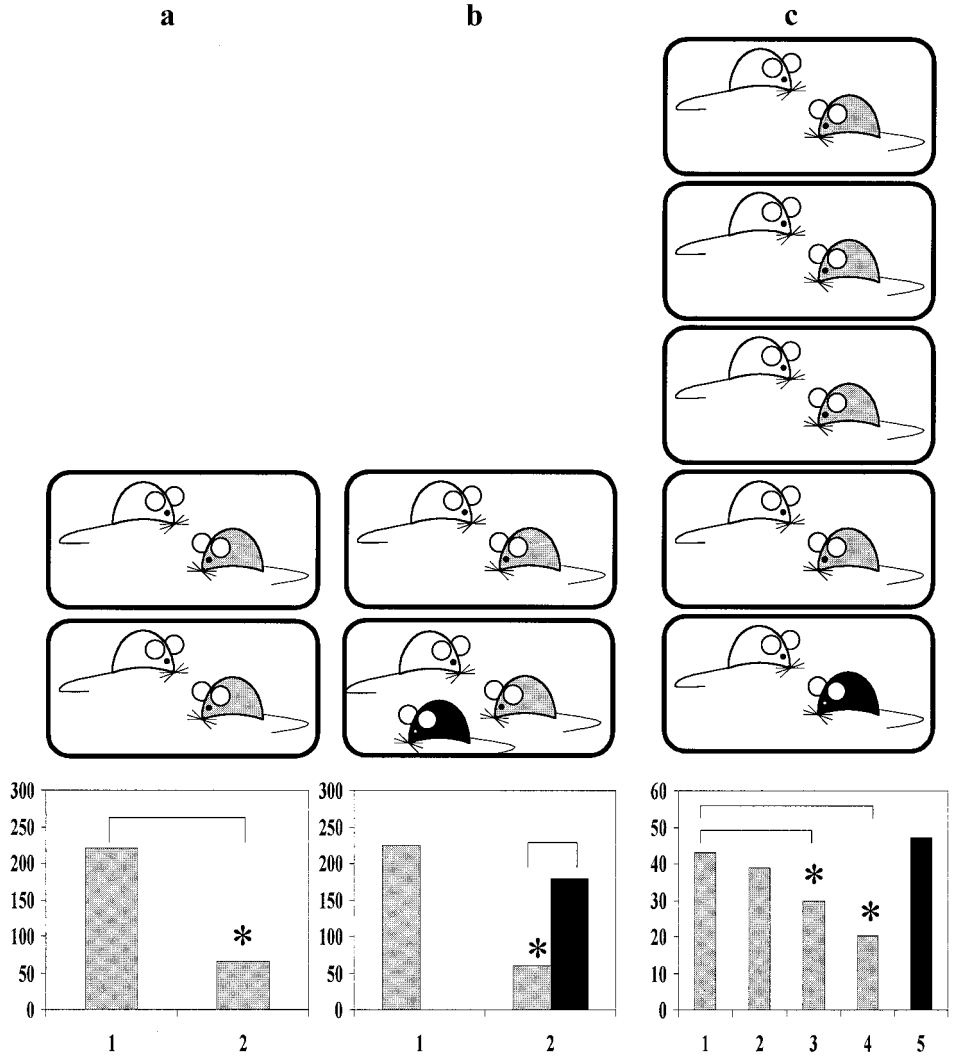

FIG. 1. Different paradigms used to measure social recognition. (a) The social recognition paradigm originally described by Thor and Holloway (116). A male rat is introduced to a novel juvenile during the first 5-min trial and the duration of olfactory investigation is measured. Thirty minutes later he is reintroduced to the same juvenile. (b) The social discrimination paradigm described by Engelmann *et al.* (36). During the second trial, the subject male is simultaneously exposed to both the familiar juvenile with whom he interacted on the first trial and a second novel juvenile. (c) The habituation–dishabituation paradigm described by Winslow (20) and Dluzen (124). The subject male is exposed to the stimulus animal during four 1-min trials, separated by 10-min intertrial intervals. During the fifth, and final, trial, the subject is presented with a novel stimulus animal. Data shown are representative of published results.

no longer recognizes the stimulus animal. The duration of the memory can be prolonged indefinitely by the repeated presentation of the same individual and can be impaired by the presentation of a novel individual between exposures to

the original animal (20, 114). Using this simple paradigm, it is possible to investigate treatments that are able to inhibit a male's normal ability to remember familiar animals at 30 min, as well as treatments able to significantly prolong the species typical recognition response for up to 2 h. The specificity of the effect can be tested by presenting a novel animal to ensure that the treatments are specifically changing social recognition rather than altering investigation time or interest in social interaction with any conspecific. Note that this short-term (i.e., roughly 60 min) test of recogntion is only one form of social memory. Recognition of mates and kin involve memories that last days, weeks, or even months and may involve cognitive and neural systems distinct from those required for short-term social recognition.

Recently, two variations of this social recognition paradigm have been suggested. In the social discrimination procedure, the subject is given a choice between a previously encountered and a novel conspecific (36). Social recognition is assessed by comparing the difference in time spent investigating the familiar and the unfamiliar stimulus animals (Fig. 1b). This modification has the advantage of allowing the test to be completed in a single follow-up session rather than requiring separate tests with familiar and novel stimulus animals. In addition, whereas the original paradigm seems to work best with retired male breeders, the modified paradigm can be used to assess recognition in sexually active males and females.

Another approach to evaluating social recognition has also been developed (30, 124). In this habituation–dishabituation paradigm, the test subject is exposed to a novel stimulus animal repeatedly for 1 min with 10-min intertrial intervals. Familiarity can be detected by reduced investigation on each trial. Following the fourth such exposure, a novel stimulus animal is used to rule out the possibility that the test animal's reduced investigation is not due to fatigue or habituation (Fig. 1c). Overall test times used in this paradigm are frequently half those required using either of the previously discussed tests, making this approach especially useful for rapid, high-throughput pharmacological or phenotypic screening studies.

Within these three basic paradigms, there are a number of variables that influence social recognition; for example, the choice of stimulus animal is critical. In the original description of the test, Thor and Holloway (117) recommended the use of juvenile males because they provided relatively neutral stimulus value, tending to provoke minimal amounts of aggression and sexual behavior from the resident subjects. Unfortunately, using a juvenile male as the stimulus animal is inconvenient for long-term studies of social recognition, especially in mice, because individual males are only appropriately aged juveniles for a very short period of time. Winslow and Camacho (20) reported that ovariectomized females make excellent stimulus animals and can be used repeatedly over weeks or even months (124). Recently, we have also determined that although intact males and females do bring about increased levels of aggression and sexual behavior in the test subjects, that it is possible to measure social recognition using even these most provocative of social stimuli (Fig. 2).

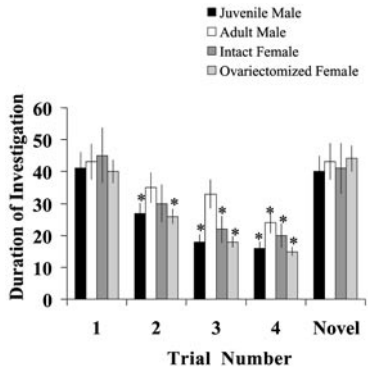

FIG. 2. Social recognition measured using different classes of stimulus animals. The graph depicts the duration of olfactory investigation (in seconds) by male mice during each of the four 1-min habituation exposures and, also during the fifth dishabituation, exposure to a novel animal. Asterisks denote trials in which there was a significant decline in the duration of investigation relative to the first trial for each stimulus condition as measured by a Student's t test, $p < .05$, following a significant single-factor (time) ANOVA.

Although this behavior has been widely described as social "memory," it differs in several ways from most other forms of learning and memory assessed in rodents. The time course of 30 min is longer than most tests of working memory but shorter than various forms of declarative, emotional, or spatial memories, which can be detected 24 h later. There is also an apparent gender difference in rat social memory. Relative to males, females have far lower levels of baseline investigatory behavior, but they retain recognition responses significantly longer (7) (Fig. 3). And, although the internal hormonal environment of the subject does not seem to have profound effects on that individual's ability to recognize previously encountered individuals, it does significantly alter his or her degree of interest in both familiar and unfamiliar conspecifics (56) (Fig. 4).

What is the salient cue used for social recognition? In rodents the signal is primarily olfactory. Lesions of the olfactory bulbs impair basic recognition responses in male rats (19, 108). And, if a resident male is exposed to either urine or soiled bedding from a stimulus animal prior to testing, there is a significantly reduced level of initial investigation, indicating that the resident male has already formed a memory for that individual's signature scent (113). Rodents possess two distinct olfactory pathways. In addition to the main olfactory system, adapted for discriminating volatile odors present in the environment, rodents also possess well-developed vomeronasal or accessory olfactory pathways for the detection of nonvolatile, species-specific pheromones (Fig. 5a). Social investigation by male rodents typically involves close following, inspection, and often licking of the anogenital region of a stimulus animal. These types of behaviors and the lack of sniffing at a distance both imply that the male is utilizing pheromonal, nonvolatile odorants as recognition cues and strongly suggest the involvement of the accessory or vomeronasal system. Because this pathway is sexually dimorphic and exquisitely sensitive

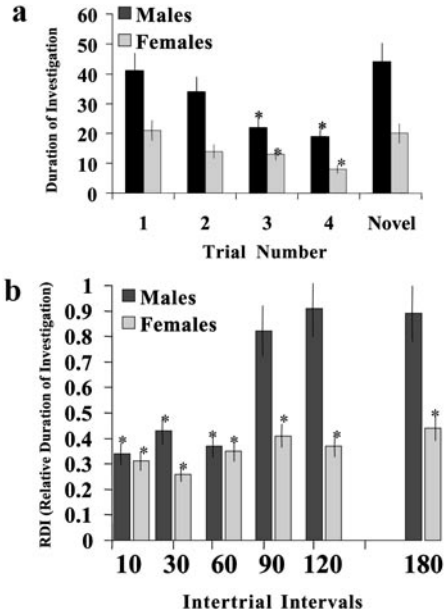

FIG. 3. Gender differences in social recognition. (a) The duration of olfactory investigation (in seconds) by male and female mice during each of four 1-min exposures to an ovariectomized stimulus mouse and also during the fifth dishabituation exposure to a novel animal. Asterisks denote trials in which there was a significant decline in the duration of investigation relative to the first trial for each stimulus condition as measured by a Student's t test, $p < .05$. Note that although baseline levels of investigation differ between intact males and females, both sexes show similar patterns of recognition. (b) The duration of investigation by male and female mice was compared after varying intertrial intervals (in minutes). For this comparison, each test animal saw the same stimulus animal for 5 min on two trials. The investigation times were converted to ratios: time spent in olfactory investigation during the second trial divided by the time spent during the first trial (97). Using these derived relative duration of investigation (RDI) ratios, values less than 0.5 typically indicate "recognition," while values close to 1.0 indicate that the subject considers the stimulus animal "unfamiliar." Note that female mice recognize individuals after intervals as long as 180 min while males fail to recognize recently encountered individuals when 90 min passes between exposures. In all cases, asterisks denote social recognition or a significant decline in the duration of investigation during the second trial ($p < .05$).

to the effects of gonadal steroids, the involvement of this system is also consistent with the dramatic sex differences in recognition described above (17). Castration, which has dramatic effects on only the accessory olfactory system, causes male rats and mice to behave very much like females when tested in the basic recognition paradigm. Testosterone replacement in these animals not only reverses the castration-induced atrophy of the accessory olfactory structures but also restores male typical recognition responses (9). Importantly, both castration and lesions of the vomeronasal organs result in only temporary loss of the ability to recognize recently encountered individuals, suggesting other pathways are able to compensate (8) (Fig. 5b). Additional evidence suggests that these compensatory pathways in the male might be similar to those utilized by females and by castrated males (26).

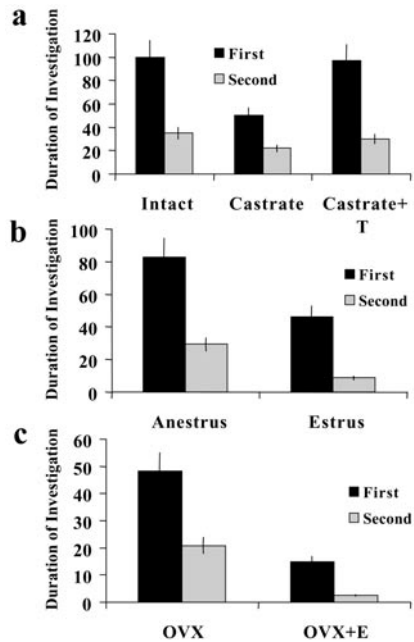

FIG. 4. Gonadal steroids and social recognition. (a) While castration drastically reduces the duration of olfactory investigation that a male rat displays toward both novel and familiar conspecifics, it does not affect his capacity to recognize previously encountered individuals. Adapted from (10). (b) Similarly, the fluctuating levels of ovarian hormones across the estrous cycle in female rats affect investigation times but not social recognition *per se.* The bars depict the duration of investigation during two trials separated by 120 min. Adapted from (37). (c) While estrogen replacement after ovariectomy dramatically reduces baseline levels of olfactory investigation in female rats, it does not diminish recognition performance. The bars depict the duration of investigation during two trials separated by 120 min. Adapted from (56).

Given that even the gross neuroanatomical structures and pathways underlying rodent social recognition still remain uncertain, it is perhaps not surprising that the specific neurochemical and neurophysiological processes underlying the recognition response are basically unknown. Dopaminergic and noradrenergic mechanisms have been suggested (30, 51–53). And, to date, NMDA- and non-NMDA-mediated glutamatergic neurotransmission as well as muscarinic acetylcholine receptor activation have been implicated (57–61). In addition to these fast, small molecule neurotransmitters, a variety of peptide neuromodulators have also been shown to have effects on social memory. And, among the neuropeptides believed to play a role in socially relevant forms of recognition, OT and AVP seem to be the most likely candidates.

VASOPRESSIN AND SOCIAL BEHAVIOR

For almost 4 decades, it has been known that AVP has central effects on learning and memory. In the 1960s DeWied found that removal of the posterior

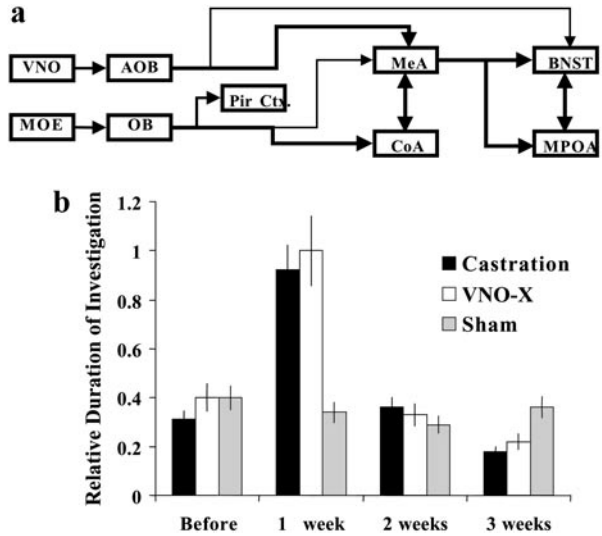

FIG. 5. Social recognition and the olfactory systems of the rodent. (a) Schematic depicting the two distinct olfactory pathways in the rat and the mouse. *Abbreviations*: VNO, vomeronasal organ; AOB, accessory olfactory bulb; MeA, medial amygdala; BNST, bed nucleus of the stria terminalis; MOE, main olfactory epithelium; OB, main olfactory bulb; Pir Ctx, piriform cortex; CoA, cortical nucleus of the amygdala; MPOA, medial preoptic area. (b) Relative duration of investigation after castration, vomeronasal organ removal (VNO-X), or sham surgery. Note that there is only a temporary deficit in social recognition after destruction of the vomeronasal pathway, suggesting the existence of a compensatory pathway. Adapted from (8).

pituitary impaired active avoidance shuttlebox performance in rats and furthermore noted that the deficit could be restored by treatment with exogenous AVP (23, 25). And in the years following that initial finding, AVP has consistently been demonstrated to facilitate active and passive avoidance conditioning through enhancements of both acquisition and consolidation processes (24, 26, 28). In addition to these effects on consolidation and retrieval, AVP has also been shown to increase the retention of paired associations by inhibiting extinction in a classic taste-aversion paradigm (110). Given the effects of AVP in these experimental paradigms, it is not at all surprising that Brattleboro rats, naturally occurring mutants deficient in AVP, also have serious memory impairments when tested on both appetitive- and aversive-conditioning tasks (12, 14, 15, 119).

In addition to its well-known effects on learning and cognition, AVP has also more recently been implicated in a variety of complex social behaviors, including territorial defense and interspecies communication (18, 49, 50, 115, 118). In golden and Syrian hamsters, dominant males mark their territories by vigorously rubbing their flanks against objects within their environment. This flank marking behavior deposits the male's scent on his surroundings and has been shown to be dependent on AVP (3, 43). Flank marking can be elicited by central injections of AVP and inhibited by central administration of a V1a

receptor antagonist (1, 45, 46, 54, 67). Consistent with its role in territorial behavior, AVP also appears to facilitate some forms of aggression and dominance and in biparental species has been shown to mediate paternal behaviors including nest defense and pup retrieval (4, 44, 92, 123, 125, 128).

In monogamous prairie voles, vasopressin has been implicated in the development of pair bonds. In this species, pair bonds usually develop after mating with the emergence of selective affiliation (measured as a partner preference) and, in males, mate guarding (measured as aggression toward an intruder). In male prairie voles, low doses of AVP (0.5 ng/h icv) facilitate formation of a partner preference and mate guarding behavior even in the absence of mating (125). A V1a antagonist given icv prior to mating prevents both partner preference formation and mate guarding without reducing mating behavior (125). The location of V1a receptors in the vole brain should indicate the neural targets for AVP agonist and antagonist effects. Prairie voles have a unique pattern of V1a receptor distribution with a high concentration of V1a receptors in the ventral pallidum, a region that should be important for reinforcement and reward (64). Overexpression of V1a receptors in this region facilitates partner preference formation in males, suggesting that this region is important for the role of AVP on pair bonding in male prairie voles. Site-specific injections of a V1a antagonist into the lateral septum appear to decrease partner preference formation. Although partner preferences must require social memory, it is not clear whether AVP or AVP antagonist effects influence the memory or the incentive value of the social partner.

OXYTOCIN AND SOCIAL BEHAVIOR

Oxytocin also has central effects on social and reproductive behaviors. Given the peptide's role in the physiological events related to birth and the onset of maternal care, it is perhaps not surprising that OT is also involved in the behavioral changes that accompany the transition to motherhood (2, 63, 64, 66). In both rats and sheep, nulliparous females are not spontaneously maternal and may actively avoid newborn offspring (89). In rats, central OT facilitates the development of nurturing behavior toward neonatal pups. Central injections of OT induce maternal behavior in nulliparous, ovariectomized, females primed with estrogen (39, 93–95) and both hypothalamic lesions that disrupt OT projections and the central administration of OT antagonists prevent the induction of naturally occurring maternal behavior (40, 90, 96). Interestingly, it seems to be only the *induction* of maternal care that is affected by these treatments since the reduction of OT neurotransmission after maternal care has already been initiated seems to be without effect (62). Unlike female rats, female laboratory mice are usually spontaneously maternal, that is, mouse maternal behavior is not induced at parturition or after pup exposure. Given the specific ability of OT to modulate the induction of maternal care, it is perhaps not surprising that mice lacking the OT peptide (oxytocin

knockout mice; OTKO) have a normal complement of parental behaviors (88, 127). Although the majority of the studies to date have examined its role in the maternal behavior of the rat, OT has also been shown to facilitate the development of maternal care in nonrodent species, including sheep (73, 75, 76). The maternal ewe forms a very specific attachment to her own offspring and will reject all unfamiliar lambs to which she is exposed. Central injections of OT, administered to nonpregnant, multiparous ewes not only reduce their natural tendency to avoid all newborn offspring, but actually facilitate both acceptance and nurturance of alien, foster lambs (71, 72, 75, 84, 85). Site-specific injections of OT into the medial preoptic area and the olfactory bulb inhibited the avoidance and rejection of an unfamiliar lamb but only injections in the PVN of the hypothalamus were effective in inducing the full suite of maternal behaviors (16, 70, 73).

In addition to fostering the development of attachment behaviors between a mother and her offspring, OT also plays an important role in the formation of the attachment of an infant to its mother. Rat pups separated from their nests produce intense ultrasonic vocalizations, protesting their isolation, and OT has been demonstrated to affect the frequency with which those isolation calls are emitted (65). Moreover, infant OTKO mice have been shown to emit far fewer calls than do control mice, perhaps suggesting that social isolation is not aversive to these animals (126). Oxytocin has also been shown to facilitate a rat pup's ability to learn to recognize olfactory stimuli associated with its mother (86, 87). Like AVP, OT has also been shown to have more general effects on other forms of memory, but, unlike AVP, which generally improves mnemonic functioning, OT enhances extinction and inhibits the acquisition of both active and passive conditioning and has been shown to impair learning processes in a variety of different paradigms (11, 13, 38, 47, 77–79, 111, 112, 120, 122).

Oxytocin has also been implicated in partner preference formation in monogamous voles. Unlike vasopressin, which facilitates aggression in males, oxytocin effects appear more robust in female prairie voles. In females, oxytocin facilitates the development of a partner preference in the absence of mating and an oxytocin antagonist prevents partner preference formation without reducing mating behavior (64). Several lines of evidence suggest that the effects of oxytocin in female voles are mediated via oxytocin receptors in the nucleus accumbens, a region with abundant receptors in the monogamous species but virtually devoid of OT receptors in other species (64).

In summary, central pathways for both AVP and OT have been implicated in various forms of memory and learning as well as complex social behaviors in a range of mammals. For a more comprehensive treatment of the central nervous system effects of these neuropeptides on learning and memory, see the 1993 review by de Wied *et al.* (27). The remainder of this review focuses on the evidence that these neuropeptides have specific effects on social recognition, a critical cognitive requirement for species-typical social behavior.

VASOPRESSIN AND SOCIAL RECOGNITION

As might be predicted from the peptide's ability to enhance passive and active avoidance learning, the subcutaneous administration of AVP facilitates social recognition even when the interval between social exposures was extended to 2 h (20). Because AVP has potent effects on territorial behavior, one might expect that AVP increased the interaction with the stranger or somehow increased the salience of meeting an intruder. It is important to note that the peptide's effects were observed after the initial social encounter rather than before exposure to the stimulus animal. Thus, the effects of AVP cannot be due to altering the stimulus properties of the first encounter with a stranger, but must reflect changes in the consolidation of information.

Interestingly, the peripheral administration of both AVP analogs and selected AVP metabolites were shown to be just as effective in enhancing social memory as was the full-length nonapeptide (103, 109). Given the limited ability of either OT or AVP to cross the blood–brain barrier, it is not clear that these peripherally administered peptides or their metabolites are binding to central nervous system receptors. Intracerebroventricular injections of AVP in doses between 0.5 and 2.0 ng have been shown to enhance recognition responses in normal male rats (83). In another study, electrical and osmotic stimulation of the SON and the PVN not only caused a measurable AVP release within the hypothalamus but also significantly improved performance on an olfactory recognition task (35). Further demonstrating a role for endogenous AVP, the ventricular administration of a selective V1a antagonist was shown to inhibit the recognition of a previously encountered juvenile after only a 30-min interexposure interval (20). And, the blockade of normal AVP neurotransmission with the central infusion of an anti-AVP serum similarly inhibited typical male recognition responses (121).

The social-memory-enhancing effects of AVP in males appear to be dependent on specific neuroanatomical structures, including the dorsolateral septum (LSD). Injections of AVP into the LSD are able to restore species-typical recognition responses to the Brattleboro rat, a naturally occurring genetic mutant, lacking the AVP peptide (34) (Fig. 6a). Local injections of low doses of AVP into the LSD are also able to prolong the duration over which normal male rats are able to recognize previously encountered individuals (Fig. 6b) while local injections of the V1a antagonist block the species-typical response at 30 min (21) (Fig. 6c). As was discussed above, the AVP innervation of the LSD is sexually dimorphic and higher in intact males than in castrates or intact females (22). To determine whether the androgen-dependent AVP processes in the LSD were involved in the male-typical recognition response, the ability of local injections of the V1a antagonist to inhibit social recognition in females and castrated males was investigated (9). These studies demonstrated that recognition in both females and castrated males was insensitive to the blocking effects of the V1a antagonist in the LSD. Moreover, testosterone replacement restored the dependence of social recognition on LSD AVP in castrated males (7). Using a slightly different experimental approach, the

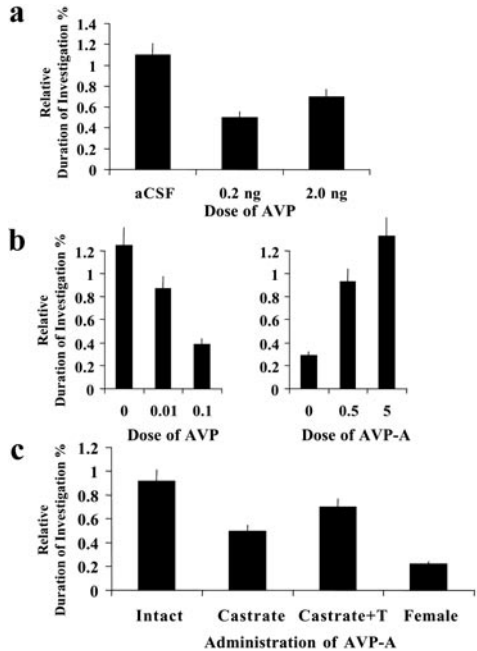

FIG. 6. Vasopressin and social recognition. (a) Relative durations of investigation for the Brattleboro rat during two trials separated by 30 min. Brattleboro rats lack AVP and exhibit impaired social memory. Note that administration of AVP (0.2 or 2.0 ng dialyzed into the lateral septum) restores social recognition. Adapted from (34). (b) Relative durations of investigation after septal injection of AVP (dose in nanograms, intertrial interval of 120 minutes). Adapted from (21). (c) Relative durations of investigation demonstrating the ability of an AVP antagonist (dose in ng, intertrial interval of 30 minutes) to inhibit social recognition. Adapted from (9).

chronic infusion of a V1a antisense oligonucleotide into the LSD was also demonstrated to disrupt normal male memory as assessed by a male's ability to recognize a familiar juvenile after a 30-min separation (81). Recently, overexpression of the V1a receptor by somatic cell gene transfer into the LSD has been shown to enhance social memory (80). Although the above studies all examined recognition responses in male rats, similar findings have also been reported in mice. While intact DBA/2 males were shown to be sensitive to the memory-inhibiting effects of septal V1a antagonism, recognition in castrated mice was determined to be independent of central AVP (10).

The ability of AVP to affect social recognition has been investigated mostly within the LSD, but a few studies have suggested that AVP may act within other central structures to mediate aspects of the recognition process. For example, microinjection of AVP antiserum into the dorsal hippocampus has been demonstrated to block species-typical male recognition responses. Injections of a V1a antagonist into the central nucleus of the amygdala interfere with the recognition enhancing effects of ventricularly injected AVP. Microinjections of AVP into the olfactory bulbs were also shown to improve normal

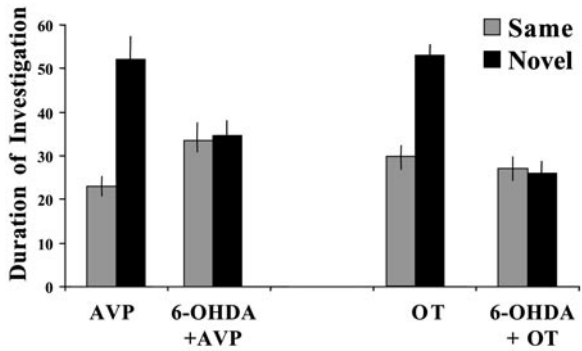

FIG. 7. Neuropeptide–noradrenergic interactions in the facilitation of social recognition. Using the social discrimination paradigm, Dluzen *et al.* (115) demonstrated that local injections of both OT and AVP into the olfactory bulbs facilitate recognition responses after an intertrial interval of 120 min. Recognition in this paradigm is denoted by a decreased duration of investigation in the "same" relative to the "novel" individual during the second trial. The ability of both OT and AVP to enhance species typical recognition responses is dependent on local noradrenergic input, as 6-OHDA lesions prevent recognition from occurring at 120 min even after neuropeptide administration. Adapted from (31).

recognition responses in male rats (32). Vasopressin effects in the bulb may be mediated by norepinephrine as the improvement in social memory requires an intact projection from the locus coeruleus (31) (Fig. 7a) and local application of AVP facilitates noradrenergic release. Clearly, longer forms of social memory, such as the Bruce effect in female mice, are dependent on noradrenergic innervation of the bulb (8, 9).

OXYTOCIN AND SOCIAL RECOGNITION

While AVP has been demonstrated to facilitate social recognition across a range of doses and routes of administration, OT has been reported to have more complex and often contradictory effects in the rat (102, 107). When administered peripherally at high pharmacological doses, OT inhibits social recognition (102). However, at lower physiological doses, the subcutaneous injection of OT actually facilitates the ability of male rats to recognize previously encountered juveniles (105). Similarly, the effects of ventricularly injected OT were found to be equally complex, with both facilitation and attenuation of social recognition observed depending on the dose administered (6). A study examining the ability of various OT-related peptides and derivatives to influence male recognition responses concluded that different groups of amino acids were capable of both enhancing and inhibiting the species typical recognition response. As was the case for AVP, injections of OT into the LSD enhanced social recognition in the rat (101). But, the lowest effective dose in this nucleus was several orders of magnitude higher than that required to facilitate recognition when OT was injected into the ventricles, making it

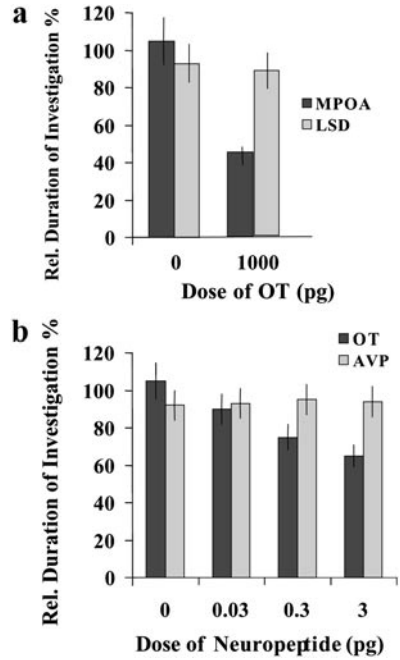

FIG. 8. Oxytocin and social recognition. (a) In data from Popik and van Ree (120), the relative duration of investigation after an intertrial interval of 120 min was decreased by OT administered into the MPOA but not when injected into the LSD of male rats. (b) In the MPOA, low doses of OT (0.3 and 3.0 ng) enhance recognition, whereas the same doses of AVP have no effect. Both figures adapted from (101).

unlikely that the effect observed was mediated through local OT receptors. On the other hand, injections of very low doses of OT were shown to be effective in enhancing the typical male recognition response when administered in the medial preoptic area, a region in which OT receptors have been demonstrated inconsistently (101) (Fig. 8a). Interestingly, AVP was not able to augment recognition when injected into this area, suggesting perhaps that social memory is modulated in both a peptide- and region-specific manner (Fig. 8b).

Unlike the differential effects of the two peptides in the LSD and the MPOA, both OT and AVP were able to enhance the ability of a male to recognize a familiar juvenile when injected into the olfactory bulbs (32). The effects of both peptides were then subsequently shown to be dependent on an intact noradrenergic projection from the locus coeruleus to the olfactory bulbs (31) (Fig. 7b). Further pharmacological investigation then established that OT's effect on social recognition in the bulbs was mediated through the activation of alpha-adrenergic receptors (33) (Fig. 9). Injections of a selective OT antagonist were unable to inhibit normal recognition at 30 min in the olfactory bulb, the lateral septum, and the medial preoptic area, further suggesting the existence of a distinct mechanism underlying the preservation and enhancement of the naturally occurring response (106). Disparities between agonist and antagonist

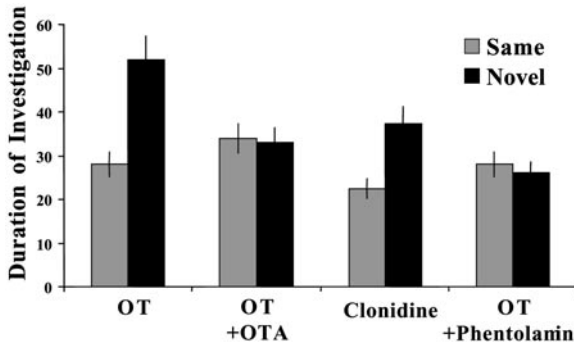

FIG. 9. Oxytocin and α-adrenergic receptors in the mediation of social recognition. Dluzen *et al.* (121) have recently used the social discrimination paradigm to demonstrate the interaction of OT and alpha-adrenergic receptors. Oxytocin (0.5 ng) enhances recognition when injected directly into the olfactory bulbs (evident by the difference between "same" and "novel" following an intertrial interval of 120 min). This facilitation of social recogntion is blocked by coadministration of an OT-specific antagonist (5.0 ng of desGly-NH_2,d$(CH_2)_5$[Tyr(Me)^2,Thr^4]OVT) but not by a V1a antagonist (data not shown). The alpha-adrenergic agonist clonidine (10 μM directly into the bulb) independently enhances social recognition. Oxytocin's ability to facilitate recognition appears dependent on alpha-adrenergic receptors, as coadministration of OT (0.5 ng) and the alpha-adrenergic antagonist phentolamine (40 nM) abolishes the OT effect. Adapted from (33).

effects are worth noting also because agonists are much less selective for the OT receptor. It is possible that OT effects in the bulb or the limbic system are mediated via V1a rather than OT receptors. Interestingly, the central administration of an OT antagonist was effective in inhibiting species typical recognition in females but not males, implying perhaps that there are sexual dimorphisms in the sensitivities to the memory enhancing properties of both AVP and OT (37).

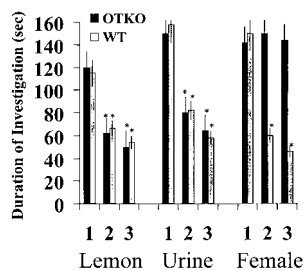

FIG. 10. Specificity of the social recognition deficit in OTKO mice. Duration of olfactory investigation during three consecutive 5-min exposures to each of three different stimuli, lemon-scented cotton balls, urine-scented cotton balls, and ovariectomized females. Both OTKO and WT mice habituate to the lemon scent and the urine, but OTKO males fail to habituate to the repeated presentation of the stimulus female. These males appear to have intact olfactory and cognitive capacities, but exhibit a specific deficit in the processing of social stimuli. Asterisks denote trials in which there was a significant decline in the duration of investigation relative to the first trial for each stimulus condition as measured by a Student's t test, $p < .05$.

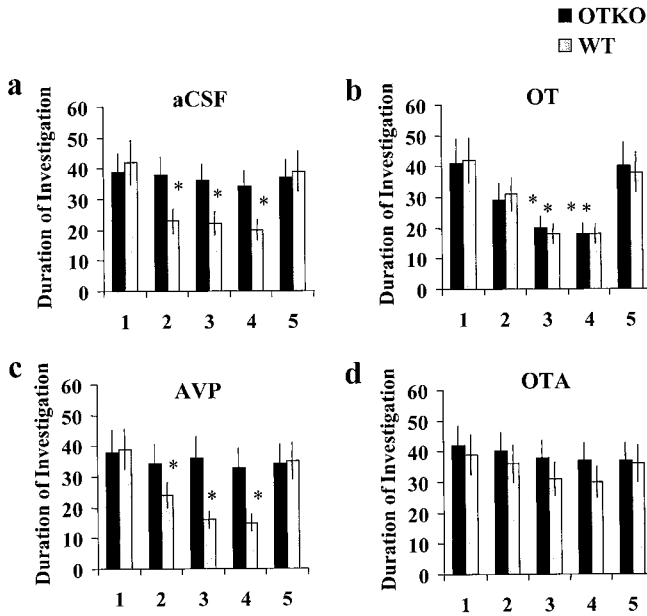

FIG. 11. The rescue of the social recognition deficit in OTKO males. (a) Social memory by WT and OTKO male mice measured as changes in olfactory investigation after icv administration of (1) aCSF, (2) OT, (3) AVP, and (4). desGly-NH_2,d$(CH_2)_5$[Tyr(Me)^2,Thr^4]OVT. Following aCSF, OTKO mice failed to recognize ovariectomized female intruders after four presentations. (b) Injection of 1 ng OT into the lateral ventricles rescued social recognition in OTKO mice measured both as a reduction in interest during repeated presentations of the same female, as well as the recovery of investigation when a new female was presented in the fifth "dishabituation" trial. (c) Administration of AVP had no significant effects on investigation by either OTKO or WT mice. (d) Injection of a selective OT antagonist had no measurable effect on olfactory investigation by OTKO mice but did significantly disrupt the decline in olfactory investigation by WT mice. Adapted from (42).

In contrast to the inconsistent findings in rats, OT has been demonstrated to be a critical mediator of social memory in the mouse. Using OTKO mice that completely lack the OT peptide, we established that OT was both necessary and sufficient for short-term social recognition in the mouse (133). These animals completely fail to recognize familiar conspecifics even after repeated encounters. This deficit does not represent an abnormality in sensory processing or a generalized impairment of learning and memory because OTKO and wild-type (WT) mice do not differ on their ability to locate hidden food, learn spatial cues for the Morris water maze, or habituate to an acoustic startle. Indeed, when scented cotton balls were used for the stimulus instead of a conspecific, subjects of both genotypes rapidly habituated to nonsocial odors, suggesting that male OTKO mice are able to process olfactory cues. OTKO mice even appear to recognize cotton balls with social scents, such as urine, when the stimulus was presented in isolation. However, they cannot use the same social cues to recognize previously encountered individuals (Fig. 10).

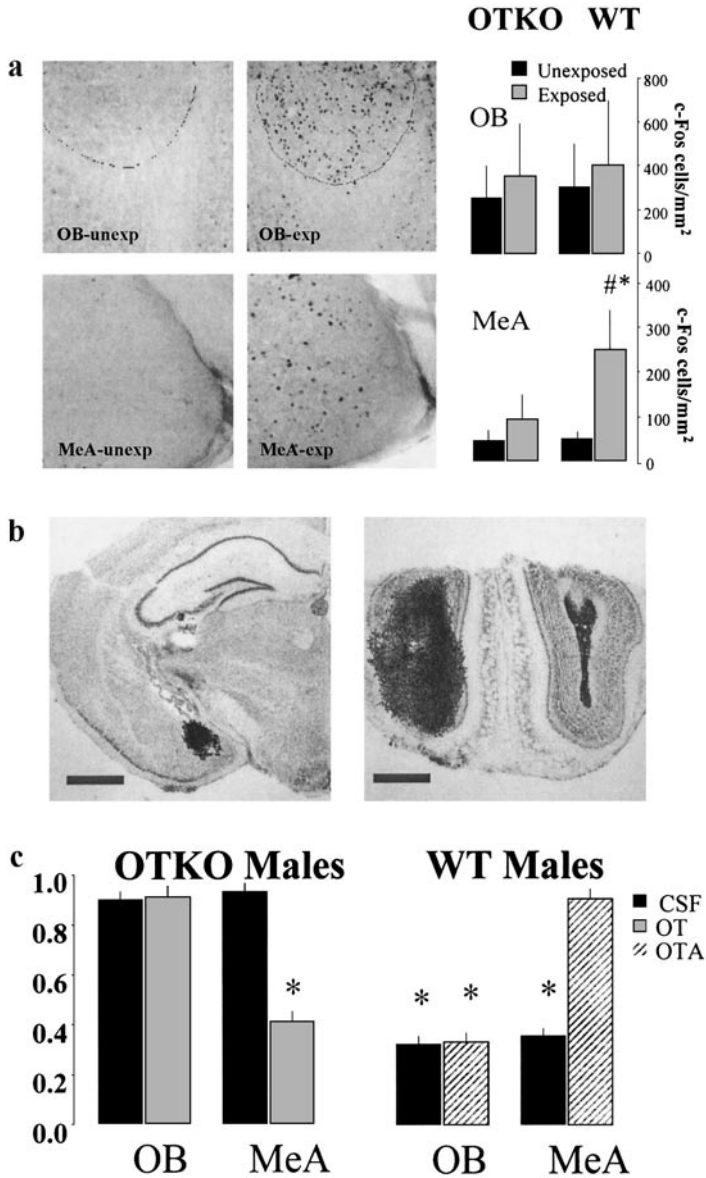

FIG. 12. cFos activation and site-specific injections of OT into the medial amygdala of OTKO males. (a) Representative photomicrographs showing c-Fos-ir in WT and OTKO males in the OB and the MeA and summary of data from both areas. Each bar represents the mean number of c-Fos positive cells/mm^2 ± SEM calculated for each genotype and treatment condition. Black bars represent unexposed animals and gray bars represent animals briefly exposed to a stimulus female. In all cases, asterisks denote significant differences between exposed and unexposed animals of the same genotype and pound signs denote significant genotype differences within the same exposure condition as assessed using the appropriate Newman–Keuls post hoc tests ($p < .05$). Note that only WT males showed a significant induction of cFos in the MeA. (b) Cresyl violet stained sections of the MeA and OB overlayed by aligned autoradiograms of adjacent sections,

Pharmacological studies in these mice have demonstrated that intracerebroventricular injections of very small doses of OT (at least 1 pg) can fully rescue the social recognition deficit (Fig. 11). Moreover, the effect appears specific for OT since injections of AVP were without effect. But, in contrast to the effects of AVP in rats, OT was only effective in mice when present during the initial social exposure. Oxytocin administered 10 min prior to the first social encounter fully restored species-typical recognition responses to the OTKO mice, while injections of OT 10 min after the first exposure did not differ significantly from injections of aCSF. Interestingly, central injections of a specific OT antagonist in WT mice also caused deficits in social recognition.

OTKO and WT mice appear to differ in the neural pathways they use to process social information. Following a 90-s social encounter, WT and OTKO mice showed different patterns of Fos induction in the brain (41). Although both genotypes activated Fos in the olfactory bulbs, lateral septum, pyriform cortex, and dorsolateral septum, OTKO males failed to induce Fos in the medial amygdala and in several downstream projections of that nucleus (Fig. 12a), including the bed nucleus of the stria terminalis and the medial preoptic area. In addition to these areas of hypoactivation in the OTKO males, the OTKO males showed a massive hyperactivation in the somatosensory cortex and in several regions of the hippocampus, including CA1, CA3, and the dentate gyrus. Although the significance of this increased activation remains unclear, these males may be compensating by recruiting alternative neural pathways.

The medial amygdala, which failed to become activated in the OTKO males, is enriched with OT receptors. To determine if OT acting on receptors within the medial amygdala was both necessary and sufficient for social recognition, we injected OT and an OT antagonist into this region (41). Very small doses of OT (0.1 pg) administered directly into the medial amygdala restored normal recognition to the OTKO animals (Fig. 12b). Identical injections into the bulbs failed to restore social recognition. Moreover, site-specific injections of an OT antagonist (0.01 ng) into the medial amygdala of WT mice reduced their ability to recognize previously encountered individuals (Fig. 12c). Injections of an OT antagonist into the olfactory bulbs of wild-type animals were without effect, effectively replicating the findings previously reported in rats.

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showing ^{125}I-labeled OTA bound to the receptors immediately surrounding the injection site. Contralateral to the injections of radioactively labeled antagonist, subjects also received injections of 4% India ink. Scale bars = 1.0 mm. (c) Site-specific injections into OTKO and WT mice. Fifteen OTKO mice were fitted with double bilateral cannulas directed at both the OB and the MeA. Subjects received injections of either CSF (black bars) or .0001 ng OT (gray bars) into one of the two neuroanatomical areas 10 min prior to the first social encounter. Fifteen WT mice were also fitted with double bilateral cannulas. The WT males received injections of either CSF (black bars) or .01 ng OTA (hatched bars) into either the OB or the MeA 10 min prior to the first social encounter. In all cases, asterisks denote social recognition or a significant decline in the duration of investigation during the second trial ($p < .05$).

SUMMARY

Oxytocin and AVP are members of a large group of ancient neuropeptides with conserved effects on a variety of mnemonic and social processes. Among their established roles in mammals, both peptides control an organism's ability to remember individuals that they have previously encountered. This form of social recognition is essential for all complex relationships, including the development of lifelong pairbonds in monogamous mammals.

The mechanisms by which AVP and OT facilitate social memory remain unclear. At a cognitive level, AVP appears more important for consolidation (in rats), whereas OT appears essential for acquisition (in mice). At this point, it is not clear whether the differences in AVP and OT effects are related to the species tested or the cognitive mechanism. The neuroanatomical distribution of receptors for both OT and AVP show profound species differences, so one might expect that these peptides will have unique cognitive and behavioral effects depending on their species-specific targets. Additional studies with AVP in mice (including mice with null mutations of AVP or the V1a receptor genes) as well as OT in rats should clarify the extent to which AVP and OT have unique effects on social recognition.

A related question is the cellular mechanism for these effects. Noradrenergic innervation of the bulb appears critical for social recognition. Kendrick and colleagues have described a cellular model for social recognition in the mouse that involves increased mitral cell to granule cell activity in the bulb, dependent on noradrenergic input (73). While AVP effects may influence this process in the bulb, OT effects on social recognition appear to be mediated via the medial amygdala. Nevertheless, OT effects may also be mediated by modulating noradrenergic activity, not only in the rat olfactory bulb (115) but in the medial amygdala of the OTKO mouse (author's unpublished data). Thus, AVP and OT may be important mostly as modulators of noradrenergic release in select neural pathways.

Now that we have two important candidates (AVP and OT) and we know some of the sites of action (i.e., medial amygdala for OT), a major area for future research will be a more careful investigation of how these neuropeptides influence cellular activity to permit social recognition. The development of transgenic mice with specific deficits in social memory provide an excellent opportunity to discover the genes, proteins, and neural circuits necessary for social recognition. Recent neuroimaging studies have begun to delineate specific "modules" for social information in the human and nonhuman primate brain. What is extraordinary about the emerging data with AVP and OT is that specific neuroendocrine modulators may have evolved earlier in phylogeny to organize social cognition and social behavior in the brain.

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