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Interplay of Oxytocin, Vasopressin, and Sex Hormones in the Regulation of Social Recognition

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Social Recognition is a fundamental skill that forms the basis of behaviors essential to the proper functioning of pair or group living in most social species. We review here various neurobiological and genetic studies that point to an interplay of oxytocin (OT), arginine-vasopressin (AVP), and the gonadal hormones, estrogens and testosterone, in the mediation of social recognition. Results of a number of studies have shown that OT and its actions at the medial amygdala seem to be essential for social recognition in both sexes. Estrogens facilitate social recognition, possibly by regulating OT production in the hypothalamus and the OT receptors at the medial amygdala. Estrogens also affect social recognition on a rapid time scale, likely through nongenomic actions. The mechanisms of these rapid effects are currently unknown but available evidence points at the hippocampus as the possible site of action. Male rodents seem to be more dependent on AVP acting at the level of the lateral septum for social recognition than female rodents. Results of various studies suggest that testosterone and its metabolites (including estradiol) influence social recognition in males primarily through the AVP V1a receptor. Overall, it appears that gonadal hormone modulation of OT and AVP regulates and fine tunes social recognition and those behaviors that depend upon it (e.g., social bonds, social hierarchies) in a sex specific manner. This points at an important role for these neuroendocrine systems in the regulation of the sex differences that are evident in social behavior and of sociality as a whole.

Keywords: estrogen, sex differences, social behavior, sociality, social learning

Social recognition, the ability of an animal to distinguish conspecifics, is an essential skill for nearly all social species (Colgan, 1983). Recognition of a conspecific allows for the initiation of an appropriate behavioral response, such as an investigative, cooperative, competitive, sexual, aggressive, or avoidant response. The importance of social recognition cannot be overlooked as it provides the basis for a range of social behaviors across varying levels of complexity. For instance, in a number of species where groups share territories familiar and unfamiliar conspecifics are discriminated between and aggression is directed mainly toward unfamiliar intruders to their territory while agonistic interactions among group members are limited. In addition, aggression toward nongroup members can also be modulated by recognition of individuals from neighboring groups of conspecifics in what is known as the dear enemy effect (Fisher, 1954). Furthermore, social recognition is crucial in the context of mate selection and sexual behavior responses. For example, in the Bruce effect, exposure of a recently inseminated female to a male mouse other than her mate results in a pregnancy block (Parkes & Bruce, 1961). Moreover, social recognition is crucial for the maintenance of social bonds such as parental bonds or mate bonds (Carter & Kerverne, 2007) and to the establishment of hierarchical organizations (Choleris, Kavaliers, & Pfaff, 2004; Timmer et al., 2011). Social recognition can also modulate social learning in some species, such as gerbils, that acquire food preferences from familiar or related conspecifics but not unfamiliar and unrelated conspecifics (Valsecchi et al., 1996) and deer mice that learn to avoid micropredators from kin and familiar individuals (Kavaliers, Colwell, & Choleris, 2005). Although the social organization of animals is influenced by recognition, the extent of and precision with which an animal recognizes another in a social context and the sensory mechanisms that it uses may vary both within and between species. Investigation into the neuroendocrinology of social recognition allows for an integrative understanding of social behavior that includes mechanistic (proximate) and functional (ultimate), evolutionary explanations (Tang-Martinez, 2003).

In this review we will focus on several neurobiological systems governing social recognition in rats and mice, the most common species of rodents used in the laboratory. In particular, we will cover the involvement of oxytocin (OT), arginine-vasopressin (AVP), and their interplay with the sex hormones, estrogens and testosterone. However, before commencing our discussion of the roles of these systems, it is necessary to: (1)

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define social recognition, and (2) establish how it is investigated in the laboratory.

Defining Social Recognition

True individual recognition, is defined as unique modifications in the way an animal behaves toward another animal based on past experiences with that specific individual (Gheusi, Bluthe, Goodall, & Dantzer, 1994). However, recognition of others may occur at a more general level, including; familiarity, social status, reproductive state, health, emotionality, and kinship (relatedness). This does not necessarily require individuals to have prior experience of each other. These other forms of social recognition are useful for identifying general characteristics that may be common across a group of individuals and are not necessarily dependent on the evaluation of cues that are individual-specific. Rather, the latter may relate to general features such as hormonal levels and their behavioral implications (e.g., anxious behavior in individuals with an over active hypothalamic-pituitary-adrenal axis). Typically, both individual-specific and class-specific recognition can operate in the regulation of social behavioral responses. For instance, even if an animal cannot distinguish between specific individuals, it may still display more social interest toward an individual that is in a receptive reproductive state. Thus, in studies of social recognition it is important to account for factors that could affect social interactions such as familiarity, gender, and relatedness, without necessarily involving true individual recognition. For example, to assess true individual recognition of a male hamster toward a conspecific male that had previously defeated him, one needs not only to assess behavioral responses toward that specific male, but also toward a male of comparable familiarity and class characteristics (e.g., dominance, testosterone levels) that had not previously defeated the experimental hamster (Lai, Ramiro, Yu, & Johnston, 2005). Although these distinctions may appear subtle, they are relevant for a thorough understanding of the proximal mechanisms of social recognition. Understanding these distinctions can avoid discrepancies in semantics that have led to heated debates in the past (e.g., Steiger & Muller, 2008; Tibbetts & Dale, 2007). Moreover, the likelihood that the neurobiological mechanisms operating at different levels of social recognition do not completely overlap reinforces the need to emphasize their distinction when designing social recognition studies and interpreting their results.

Assessing Social Recognition

A number of species of rodents including mice, rats, gerbils, deer mice, voles, and hamsters have been shown to demonstrate social recognition in a laboratory setting (Halpin, 1986). Typically, in laboratory rodents *familiarity recognition* is assessed more often than true individual recognition, and is termed generally as social recognition. Familiarity recognition is usually measured through the use of either the habituation/dishabituation paradigm or the social discrimination paradigm. These paradigms take advantage of the innate tendency of rodents to investigate an unfamiliar individual more than a familiar individual. The most commonly used method of investigating social recognition is the habituation/dishabituation procedure (see Figure 1) (Gheusi et al., 1994). The first step involves the presentation of a stimulus rodent, either once (e.g., Thor, Wainwright, & Holloway, 1982) or multiple times (e.g., Choleris et al., 2003), to an experimental rodent. The experimental rodent normally shows habituation to the stimulus, which is reflected in a reduction of its social investigative response on successive presentations of the stimulus animal. In the second step the presentation of a different conspecific to the experimental rodent usually elicits a dishabituation response returning social investigation to initial levels. A differential behavioral response toward the novel social stimulus is inferred as social recognition in this paradigm. However, desensitization to the testing procedure because of repeated testing may conceal social recognition related behavioral changes and may be considered an inherent disadvantage to the habituation/dishabituation procedure (Engelmann, Wotjak, & Landgraf, 1995). In addition, complications may arise in the interpretation of results when pharmacological manipulations are

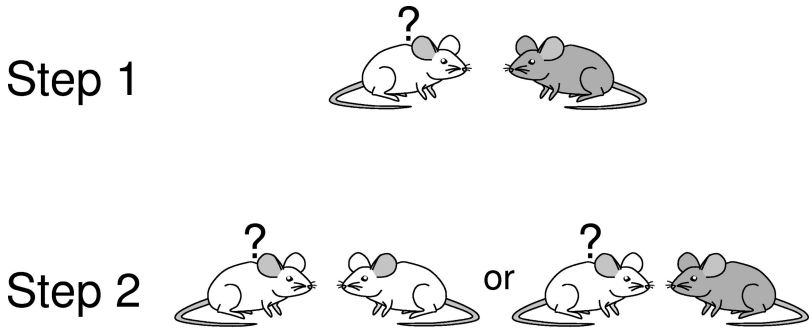

Figure 1. Social recognition: habituation/dishabituation paradigms. Step 1 involves the preexposure of the experimental subject to a conspecific (gray), either once or repeatedly. Step 2 involves presentation of either a novel (white) or the same, familiar (gray) conspecific. Repeated exposure to the same conspecific normally results in a reduction in social investigation (habituation). Presentation of a novel conspecific results in a return to the initial level of investigation (dishabituation). Habituation can result from either desensitization to the procedure and/or recognition of the now familiar conspecific. Dishabituation is considered to prove recognition of familiar versus novel conspecific. Although dishabituation is considered to rule out satiation or boredom, it may also represent sensitization to the procedure. This paradigm can be carried out with either actual animals or their odors.

involved, because testing for habituation/dishabituation occurs at different time points after drug administration.

Although somewhat less utilized than the habituation/dishabituation procedure, the social discrimination paradigm (see Figure 2) assesses social recognition in a more direct fashion and avoids some of the potential confounds in the habituation/dishabituation paradigm. In this paradigm the animal is presented with a simultaneous binary choice between a novel conspecific and a familiar one (Choleris et al., 2006; Engelmann, Hadicke, & Noack, 2011). This method, conceptually similar to other nonsocial choice tests such as object or food recognition (e.g., Choleris et al., 2000; Phan, Lancaster, Armstrong, Maclusky, & Choleris, 2011), allows social recognition to be assessed within the same test. Furthermore, the social discrimination paradigm appears to be more sensitive than the habituation/dishabituation procedure, because animals that were observed to possess no social recognition when tested in the habituation/dishabituation showed social recognition in the social discrimination paradigm (Choleris et al., 2006; Engelmann, Wotjak, & Landgraf, 1995).

For both paradigms, stimulus animals, exposure times, and intertrial intervals times may be adjusted according to the particular goal of the study. Because familiarity and individual identity, are manipulated in these paradigms conclusions about true individual recognition cannot be soundly asserted. It is likely that familiarity recognition and true individual recognition may be at play in both the habituation/dishabituation and the social discrimination procedures. Accordingly, and to keep in line with the terminology used in other studies, we refer to the results of these paradigms as measures of social recognition or familiarity recognition for the remainder of this review.

To distinguish the presence of and changes in social recognition from modifications of cognitive or physiological processes, a variety of appropriate controls are warranted. For instance, olfaction tests should be conducted to determine whether the presence or absence of social recognition may be explained by changes in olfactory sensitivity. These can be done using the same habituation/dishabituation procedures or social discrimination procedures with nonsocial odors (e.g., Choleris et al., 2011). Furthermore, other types of learning processes may contribute to social recognition; thus, additional tests such as object recognition and spatial learning tasks should be administered to distinguish the specific effects on social recognition from those on other types of learning taking place (e.g., Phan, Lancaster, Armstrong, Maclusky, & Choleris, 2011). In addition, an extensive ethological analysis of behavior can help clarify whether changes in social investigation were secondary to changes in aspect of behavior such as social interest, general activity levels, and so forth (e.g., Choleris et al., 2003, 2006; Phan, Lancaster, Armstrong, Maclusky, & Choleris, 2011).

Oxytocin and Social Recognition

OT is a small neuropeptide consisting of nine amino acids configured as a ring and tail. The main sources of OT include the magnocellular neurons of the hypothalamic paraventricular and the supraoptic nuclei (PVN and SON), and the parvocellular neurons of the PVN. OT is transported into the posterior pituitary gland via projections from the magnocellular neurons (Nilaweera et al., 2008). From the pituitary gland OT is released into general circulation to act as a neurohormone that is involved in birth and lactation. Alternatively, parvocellular neurons project to different brain areas, where OT is released to act as a neuromodulator (reviewed in Gimpl & Fahrenholz, 2001). The OT receptor (OTR) belongs to the G protein-coupled receptor family and is, to date, the only known form of the receptor. OTRs are found in many brain regions that are known to be either directly or indirectly involved in social behavior. Thus, not surprisingly, OT has been shown to play a role in several features of sociality (reviewed in Donaldson & Young, 2008), including social recognition.

Initial investigations into the involvement of OT in social recognition yielded conflicting results. Both low doses of OT antagonists (Popik & Vetulani, 1991) and OT and OT related peptides (Popik, Vetulani, & van Ree, 1992) administered systemically in rats after the first social exposure in a two-trial habituation paradigm facilitated the memory for a previously presented juvenile rat. In contrast, high doses of OT, above physiological levels,

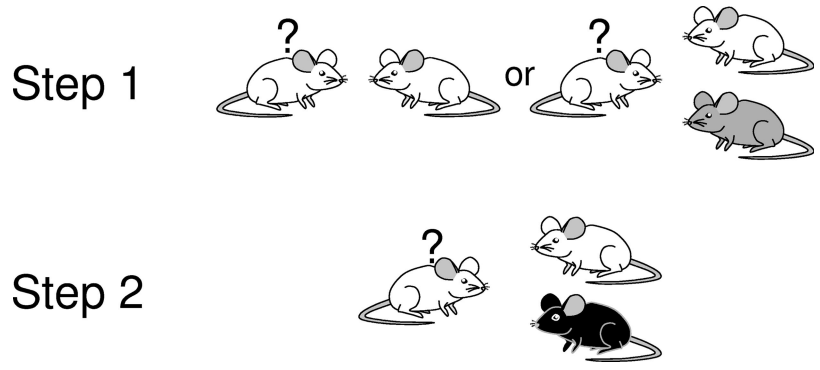

Figure 2. Social recognition: discrimination paradigms. Step 1 involves the presentation (once or repeated) to the experimental animal (white) of either one (white) or two (white and gray) conspecifics. Step 2 involves the simultaneous presentation of a familiar (white) and a novel (black) conspecific to the experimental animal (white). In Step 2 the experimental animal will typically investigate the novel conspecific more than the familiar conspecific. This is considered indicative of recognition of familiar versus novel conspecific. This paradigm can be conducted with either whole animals or their odor cues.

impaired social recognition (Dantzer, Bluthe, Koob, & Le Moal, 1987; Popik & Vetulani, 1991). These inconsistencies were attributed mainly to differences in effects on social memory by the varying OT-related peptides utilized across the experiments (Popik, Vetulani, & van Ree, 1996). Furthermore, any actual effects on behavior were difficult to ascertain, since the systemically administered drugs in those experiments only partially crossed the blood–brain barrier (see discussion in Popik, Vos, & van Ree, 1992). Intracerebroventricular administration of an OT antagonist immediately after first exposure impaired social recognition in female rats (Engelmann, Ebner, Wotjak, & Landgraf, 1998). In accordance, low doses of OT seem to enhance social recognition, because administration of the drug immediately after an encounter with a juvenile reduced the investigation time of the experimental rodent toward the same juvenile during a second encounter 120 min later. Furthermore, this improved social recognition could be reversed by the simultaneous administration of an OT antagonist (Benelli et al., 1995). These studies suggested that physiological doses of OT could facilitate social recognition in both female and male rats.

With the advent of OT knockout (KO) mice (OTKO), results of a number of studies have shown that OT is essential for familiarity recognition (Choleris et al., 2003; Choleris et al., 2006; Ferguson et al., 2000). Unlike their wild-type (WT) littermates, male and female OTKO mice fail to habituate to repeated presentations of an individual mouse and do not show increased investigation upon the presentation of a novel mouse (Choleris et al., 2003; Ferguson et al., 2000). In addition, OTKO mice, which are unable to distinguish between familiar and unfamiliar individuals, cannot perform the social discrimination test successfully (Choleris et al., 2006). Thus, it is evident that OTKO mice lack the ability to recognize familiar and unfamiliar conspecifics. Social recognition can be recovered in these OTKO mice by infusion of OT into the lateral ventricles of the mice before (but not after) their initial interaction with the conspecific individuals (Ferguson, Aldag, Insel, & Young, 2001). These studies suggest that OT functions to facilitate acquisition of the social recognition rather than mediating consolidation or retrieval. Furthermore, the fact that social recognition in adult OTKO mice may be recovered by OT administration suggests that the social memory impairments of these transgenic mice are because of the absence of OT activity in the brain rather than disruptions to normal development.

Additionally, males of two separately generated strains of oxytocin receptor knockout (OTRKO) mice showed impairment in social recognition, further supporting a role for OT in social recognition (Lee, Caldwell, Macbeth, Tolu, & Young, 2008; Takayanagi et al., 2005). Conditional partial forebrain OTRKO mice were derived. These mice showed reduced binding of OTR in the lateral septum, hippocampus, and ventral pallidum at the approximate age of weaning (Lee et al., 2008). During the second trial of a two trial habituation/dishabituation social recognition paradigm, the partial forebrain OTRKO mice showed a reduction in social investigation regardless of whether a familiar or a novel social stimulus was presented, demonstrating an impairment in social memory. However, it seems that with multiple presentations their social recognition deficit may be rescued, because when tested a week later in a habituation/dishabituation paradigm with four habituation sessions before dishabituation testing, the partial forebrain OTRKO mice performed normally. In comparison, male OTRKO mice that were OTR deficient in all tissues were impaired in their ability to habituate to familiar individuals, equally investigating both novel and familiar conspecifics (Lee et al., 2008; Takayanagi et al., 2005), which is in accordance with the results of previous studies using OTKO mice. The effects described in these studies seem to be specific to social recognition since neither OTKO mice nor the conditional OTRKO mice were impaired in general behaviors (i.e., investigation of nonsocial stimuli, grooming, general activity levels), spatial learning, motor functions or discrimination of social or nonsocial olfactory cues (Choleris et al., 2003; Ferguson et al., 2000; Kavaliers et al., 2003; Lee et al., 2008).

It is important to note that OTR binding was still retained in the medial amygdala, the olfactory bulb, olfactory nucleus, and neocortex in these partial forebrain OTRKO mice. The limited impairment in social recognition of these mice is in accordance with a number of studies showing OT action at the medial amygdala is essential for social recognition in mice (Choleris et al., 2007; Ferguson et al., 2001). In rodents, the medial amygdala integrates socially relevant olfactory inputs from the main and accessory olfactory system (Beauchamp & Yamazaki, 2003; Dulac & Torello, 2003; Johnston & Peng, 2008; Kang, Baum, & Cherry, 2009). Social recognition can be restored in OTKO mice by the infusion of OT into the medial amygdala and is disrupted by the administration of OT antagonists and OTR antisense DNA into the medial amygdala of WT mice (Choleris et al., 2007; Ferguson et al., 2001). Administration of an OT antagonist into the medial amygdala also resulted in the suppression of immediate early genes that would be normally expressed in response to biologically relevant chemical signals from conspecific mice (Samuelsen & Meredith, 2011). Moreover, social hierarchy-related memory for specific dominant males was reduced by infusion of an OTR antagonist in the medial amygdala immediately after memory acquisition (Timmer et al., 2011). Hence, the medial amygdala seems to play a crucial role in OT mediation of social recognition, including true individual recognition.

Brain regions other than the amygdala have been shown to play a role in social recognition. Social recognition was also enhanced in rats also by an infusion of OT in the lateral septum (LS) (Popik & van Ree, 1991; Popik et al., 1992; Van Wimersma-Greidanus & Maigret, 1996), medial preoptic area of the hypothalamus (Popik & van Ree, 1991), and in the ventral hippocampus (Van Wimersma-Greidanus & Maigret, 1996). However, in all of these brain regions, the effects of OT on social recognition could not be reversed by a single dose of an OTR antagonist. Perhaps these brain areas may be capable of facilitating, but are not necessary for, social recognition. Social recognition memory is also improved by OT administration into the olfactory bulbs of rats (Dluzen, Muraoka, Engelmann, & Landgraf, 1998; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). Again, in this case social recognition is not impaired by the administration of OT antagonists at the olfactory bulb (Dluzen, Muraoka, Engelmann, Ebner, & Landgraf, 2000). In addition, social recognition in OTKO mice is not rescued with delivery of OT at the olfactory bulb in a habituation/dishabituation test (Ferguson et al., 2000). A possible explanation is that the facilitative effects of OT on social recognition in the olfactory bulb are mediated by an enhancement of norepinephrine action at the α-, but not β-, adrenoceptors. Overall, it seems that in mice OT/OTR action at the medial amygdala is both necessary and sufficient for social recognition, while OT in

other areas of the brain, such as the lateral septum and the olfactory bulbs, only appear to modulate social recognition. Thus, in general, OT appears to be essential for social recognition and is dependent on OT/OTR action at the medial amygdala (Choleris et al., 2007; Ferguson et al., 2000, 2001). It seems that OT also affects social recognition in rats and the medial amygdala plays a role as well, but to what extent and in what specific brain regions this effect is being mediated is still to be clarified in this species. In addition, it appears that OT-mediated effects on social recognition are not sexually dimorphic in mice (Choleris et al., 2003; Choleris et al., 2007; Engelmann et al., 1998; Ferguson et al., 2001) and rats (Benelli et al., 1995; Engelmann et al., 1995), which is unlike the effects of vasopressin on social recognition (described in the next section) or OT on other social behaviors.

An ecologically important consequence of the OTKO mice's impairment in social recognition was shown in investigations of a common cost of sociality: the increased risk of acquiring parasites and other pathogens from others. Mice and other species of rodents are typically proficient at identifying and avoiding parasitized conspecifics and at developing aversive responses to them (Kavaliers, Choleris, Ågmo, Muglia, Ogawa & Pfaff, 2005). Female OTKO mice, instead did not show such discrimination and avoidance of the odors of either subclinically nematode or louse infected male mice (Kavaliers et al., 2003, 2005, 2006). In addition, OTKO females displayed attenuated aversive responses and did not distinguish between the odors of familiar and novel infected males. Similarly, OTKO males failed to recognize and display aversive responses to the odors of other nematode or louse infected males and could not modulate their aversive response on the basis of social familiarity (Kavaliers, Choleris, Agmo, & Pfaff, 2004). The specific involvement of OT in the recognition of infected conspecifics was further confirmed with central administration of selective OT antagonists to nongenetically modified male and female mice (Kavaliers et al., manuscript in preparation; reviewed in Kavaliers & Choleris, 2011) and was extended to male rats and illness odors (Arakawa, Arakawa, & Deak, 2010). Hence OT seems to be part of the evolutionarily conserved neuroendocrine mechanisms by which male and female mice and rats can distinguish socially salient odors and avoid parasitized and sick conspecifics (Kavaliers & Choleris, 2011).

Arginine-Vasopressin and Social Recognition

AVP is a neuropeptide that is structurally and genetically similar to OT (Ludwig & Leng, 2006) and is thought to be derived from the same ancestral peptide, vasotocin, as a result of a gene duplication event (reviewed in Frank & Landgraf, 2008). AVP is synthesized predominantly in magnocellular and parvocellular neurons of the PVN and SON of the hypothalamus. As part of the hypothalamic-neurohypophysial axis magnocellular neurons release vasopressin via the posterior pituitary into the bloodstream where it acts mainly as the antidiuretic hormone. Parvocellular neurons in the region of the PVN release vasopressin along the hypothalamic-pituitary-adrenal axis. Major extrahypothalamic sources of vasopressin include the bed nucleus of the stria terminalis (BNST) and the medial amygdala (Bielsky et al., 2004; reviewed in Frank & Landgraf, 2008). AVP is known to be involved in a range of social behaviors in rodents (reviewed in Donaldson & Young, 2008), including social recognition (Bielsky, Hu, Ren, Terwilliger, & Young, 2005; Bluthe, Suarez, Fink, Roques, & Dantzer, 1993; Popik et al., 1992). AVP involvement in social recognition was made apparent when subcutaneous administration of AVP (Dantzer et al., 1987) or AVP-derived peptides (lacking peripheral activity) immediately after the first exposure to a juvenile conspecific, prolonged the memory for that conspecific in adult male rats (Sekiguchi, Wolterink, & van Ree, 1991). Additionally, Brattleboro male rats, which have a spontaneous mutation that causes a deficiency in AVP show a significant deficit in social recognition (Feifel et al., 2009). The enhancing effect of AVP on social memory could be reversed with the use of an AVP antagonist (Dantzer et al., 1987), supporting a key role for endogenous AVP in the social memory of a familiar conspecific. Because the OT receptor has only a 10-fold greater affinity for OT than AVP, AVP may act on OT receptors to mediate its effects on social recognition (Gimpl & Fahrenholz, 2001). However, this only partially explains the effects of AVP because there is growing evidence to support an AVP receptor specific role in social recognition. Vasopressin acts on two receptors in the brain, vasopressin 1a receptor (V1aR) and vasopressin 1b receptor (V1bR), both of which are G protein-coupled membrane receptors. Each receptor differs in its pharmacological properties, tissue distribution and secondary messenger cascades, and therefore produces varying effects. Of these two receptors, V1a seems to play a more prominent role in the modulation of social behavior, in a manner that is likely linked to differences in brain distribution and gene (*avpr1a*) polymorphism (reviewed in Donaldson & Young, 2008). Social recognition in male V1aR KO (V1aRKO) mice is impaired (Bielsky et al., 2004): regardless of their familiarity with the stimulus mouse, male V1aRKO mice did not habituate with repeated presentations of an individual and retained high social investigation throughout the entirety of the habituation-dishabituation test (Wersinger et al., 2004). In contrast, social recognition in male V1bR knockout (V1bRKO) mice seems to only be partially impaired (Wersinger, Ginns, O'Carrol, Lolait, & Young, 2002; Wersinger et al., 2007). Compared to WT animals, male V1bRKO mice took more time to habituate to familiar females, and unlike the wild type animals they did not preserve the memory for a familiar female after a 30 min delay (Wersinger et al., 2002). However, after multiple presentations, V1bRKO mice did manage to habituate to a familiar individual, and even showed dishabituation upon the introduction of a novel mouse. Hence, relative to WT mice, V1bRKO mice are impaired in social recognition, but under "easier" testing conditions that include increased habituation sessions and shorter time intervals between habituation and testing, they are still able to distinguish between familiar and unfamiliar conspecifics (Wersinger et al., 2004). Thus, the V1bR may not be as important for social recognition as the V1aR, supporting a receptor subtype dependent effect of AVP on social behavior in mice.

A number of studies have implicated several brain regions for the site of action for AVP regulation of social recognition. In adult rats, a rise in intracerebral AVP through stimulation of the SON enhanced the acquisition of social recognition (Engelmann & Landgraf, 1994b). In addition, memory for a familiar juvenile in adult male rats was prolonged by intracerebroventricular infusion of AVP immediately after social interaction with that juvenile conspecific (Bluthe & Dantzer, 1992; Le Moal, Dantzer, Michaud, & Koob, 1987). Administration of AVP antiserum could diminish the prolonging effect of AVP (Van Wimersma-Greidanus & Mai-

gret, 1996) that supported a brain based mechanism of AVP involvement in social recognition. Subsequently, many brain regions have been implicated in AVP-mediated social memory.

The lateral septum (LS), a region with high V1aR expression, has been shown to be the site of AVP mediated effects on social recognition in male rats. Social memory of a juvenile conspecific was improved in both the habituation/dishabituation and the discrimination paradigm tests when AVP was administered into the LS of rats directly after an initial social interaction with that juvenile (Appenrodt, Juszczak, & Schwarzberg, 2002; Dantzer, Koob, Bluthe, & Le Moal, 1988; Engelmann & Landgraf, 1994a; Everts & Koolhaas, 1997). Endogenous release of AVP in the LS correlated with social discrimination in a manner that could be partially blocked by infusion of an AVP antagonist (Engelmann & Landgraf, 1994). Consistently, early stress induced impairment in social recognition was accompanied by a lack of AVP release in the LS of male rats (Lukas et al., 2011). Moreover, social memory in male rats was impaired and AVP-induced enhancements were reversed upon the administration of either AVP antiserum (Van Wimersma-Greidanus & Maigret, 1996), V1aR gene targeted antisense DNA (Landgraf et al., 1995), or AVP V1 receptor antagonist (Appenrodt et al., 2002; Dantzer et al., 1988; Everts & Koolhaas, 1999) into the LS (Landgraf et al., 1995; Popik & van Ree, 1992). Reversal of AVP-mediated improvements in social memory via AVP antagonist V1 administration in the septum (Appenrodt et al., 2002; Popik & van Ree, 1992) supports a role for endogenous AVP in social memory through AVP receptor specific mechanisms in the LS. Accordingly, transfer of the gene for V1aR into the LS of male rats enhanced social memory as evidenced by the fact that the rats could discriminate between a familiar and an unfamiliar juveniles even 2 hr after initial exposure, when the control rats no longer showed social recognition. The enhancement in social memory was comparable to the effects seen by an infusion of AVP into the LS and likewise could be reversed by a V1aR (but not an OTR) selective antagonist (Landgraf et al., 2003). The effects of AVP receptor antagonists suggest that AVP-induced social recognition cannot be explained by cross-activation of OTR (also expressed in the LS) alone (Gimpl & Fahrenholz, 2001). AVP mediated effects on social recognition have also been shown to occur in the LS of mice. In V1aRKO male mice, re-expressing the V1aR gene in the LS could rescue social recognition impairment and overexpression could enhance social recognition in WT mice (Bielsky et al., 2005). In summary, there is compelling evidence to support a specific and distinct role for AVP and the V1aR subtype in the LS in the involvement of social recognition in both mice and rats.

There is also evidence that AVP modulates conspecific social recognition at the level of the olfactory system (Wacker & Ludwig, 2011). Recently, an intrinsic vasopressin system has been discovered in the olfactory bulb that is involved in social recognition. Unlike other regions of the brain, this population of vasopressin neurons is not sexually dimorphic in rats (Tobin et al., 2010). Previously, it was shown that infusion of AVP in the olfactory bulb enhanced social memory in male rats in a manner that was not countered by either OT or AVP antagonists (Dluzen, Muraoka, Engelmann et al., 1998; Dluzen, Muraoka, & Landgraf, 1998). The failure to impair social memory with AVP antagonists was initially explained by the mediation of AVP facilitator effects by norepinephrine action at the α-adrenoceptor in the olfactory bulb (Dluzen, Muraoka, & Landgraf, 1998). However, recently, a more readily diffusible nonpeptide V1 receptor antagonist impaired social recognition at the level of the olfactory bulb. The antagonist was bilaterally infused into the main olfactory bulb and impaired the ability of male rats to discriminate between familiar and unfamiliar conspecifics after only a 30 min retention interval. Furthermore, infusion of a virus containing a V1a receptor siRNA into the olfactory bulb led to similar results and disrupted normal social memory retention over this short time interval. In addition, transgenic mice with abolished AVP cells in the olfactory bulb via insertion of human diptheria toxin receptor in the AVP promoter region showed similar impairment of social recognition (Tobin et al., 2010). These results suggest that AVP in the olfactory bulb may also facilitate social odor memory in mice and in rats.

AVP-mediated effects on social recognition have been shown to be present in the hippocampus as well. Delivery of antiserum to the dorsal or ventral hippocampus posthabituation impaired social recognition in male rats (Van Wimersma-Greidanus & Maigret, 1996). There is also limited evidence for an effect of AVP at the level of the medial amygdala. Infusion of a V1aR and V1bR antagonists at the medial amygdala blocked the recognition of, and aversive responses to, sickness odors in juvenile but not in adult male rats (Arakawa et al., 2010). Overall, it seems that the AVP action in the LS is necessary and sufficient for AVP mediation of social recognition in both rats and mice, with a dependence on V1aR expression in mice (Bielsky et al., 2005). However, there may be additional brain regions in both mice and rats that in varying degrees provide additional mechanisms by which social recognition is facilitated through AVP action, including the olfactory bulb and hippocampus.

In mice, AVP antagonist in the LS blocked social memory but did not affect object or spatial memory, suggesting that the facilitative action of AVP in the LS on social recognition may be specific for social memory, (Bielsky et al., 2005). Likewise the effects of AVP antagonists in the olfactory bulb seemed to be specific to social memory since object recognition, locomotor activity or anxiety related behaviors were not affected (Everts & Koolhaas, 1999). Furthermore, aside from impaired social recognition and reduced anxiety-like behaviors in V1aRKO male mice, their locomotor activity, olfaction, sensorimotor gating, and spatial learning task performance were normal (Bielsky et al., 2004). Moreover, recovery or improvement of social recognition in mice through re-expression of the AV1aR gene in the AV1aRKO and in the AV1aRWT, respectively, did not affect other behaviors tested, such as anxiety-like behaviors and olfactory learning (Wersinger et al., 2007). The AV1bRKO mice were impaired in social behaviors such as social recognition, aggression and social motivation but retained spatial learning ability, olfactory ability, predatory behavior, and defensive aggressive behavior (reviewed in Caldwell, Lee, Macbeth, & Young, 2008; Wersinger et al., 2002; Wersinger et al., 2004).

In contrast to OT, AVP seems to be more essential for social recognition in males than in females. This may be expected considering that AVP expression is greater in male brains than in female brains across a number of species (reviewed in De Vries, 2008) and that in many cases AVP is associated with male-typical social behaviors such as male reproduction, aggression and territoriality (reviewed in Donaldson & Young, 2008). Similar to males, female mice show an improvement in social recognition

upon peripheral administration of AVP (Bluthe & Dantzer, 1990; Bluthe, Schoenen, & Dantzer, 1990). However, there was no effect on social recognition in the female rat upon administration of an AVP antagonist, whereas in male rats social recognition was impaired (Bluthe & Dantzer, 1990; Bluthe et al., 1990; Engelmann et al., 1998). Thus, AVP appears to be essential to male mice and rats for social recognition, while in females it may only play a facilitatory role (Bluthe & Dantzer, 1990; Engelmann et al., 1998).

Estrogens and Social Recognition

Estrogens have been shown to influence social recognition in a number of experimental paradigms. Female mice (Sanchez et al., 2009), show enhanced performance in the context of the habituation/dishabituation social recognition paradigm during the proestrous phase of the estrous cycle, when levels of circulating estrogens and progesterone are high (Walmer et al., 1992). As well, the long term recall of social recognition memory seems to be dependent on estrous cycle. Thus, it appears that social recognition ability in mice is at its peak when females are reproductively active. The impairment in social recognition for a familiar conspecific caused by ovariectomy in mice can be reversed with the administration of estrogens in mice (Tang et al., 2005). There is some evidence that rats also show improvements in social recognition at the proestrus phase (Engelmann et al., 1998) and impairments because of ovariectomy can be recovered by the delivery of estrogens (Hlinak, 1993) or with estrogens and progesterone (Spiteri & Agmo, 2009). These results suggest that the effects seen at proestrous are mediated by estrogens in both mice and rats.

Estrogens target several receptors, including the two classic estrogen receptors (ER) alpha (ERα) and beta (ERβ) and at least one G-protein-coupled receptor (reviewed in Choleris et al., 2009). The effects of estrogens on social recognition are dependent on the timing of testing, timing of administration, dosage of drug administered and the differential activation of estrogen receptors. When the ERα selective agonist, 1,3,5-tris(4-hydroxyphenyl)-4-propyl-1H-pyrazole (PPT), was administered to both gonadally intact and ovariectomized females 48 hr before testing (a time consistent with estrogen's genomic effects), it improved social recognition at low doses, but impaired it at high doses. The ERβ agonist, WAY-200070, was also able to improve social recognition in gonadally intact and OVX female mice when administered 48 hr before testing (Cragg, Fissore, Pfaff & Choleris, unpublished data).

Studies using KO mice further support a role for both ERα and ERβ in social recognition. Male ERαKO mice showed no behavioral changes in response to a novel mouse in a habituation/dishabituation paradigm, demonstrating an impairment in social recognition (Imwalle, Scordalakes, & Rissman, 2002). Likewise, both ERαKO and ERβKO female mice showed impairments in the habituation/dishabituation paradigm resembling those of OTKO female mice (Choleris et al., 2003). Later, the use of a binary choice discrimination paradigm demonstrated that ERβKO female mice are partially impaired in social recognition, while ERαKO female mice are completely unable to distinguish between conspecifics (Choleris et al., 2006). ERαKO females tested in their home cage devoted equal amounts of time to investigating a familiar and an unfamiliar ovariectomized mouse. The ERβKO mice, however, spent ~70% of their social investigation time sniffing at the novel, rather than the familiar, mouse, suggesting only a partial impairment in social recognition, since the investigation of the novel stimulus was still above random, yet it was significantly less than WT female littermates, who spent 86% of their social time investigating the novel mouse. Thus, differing degrees of impairment in social recognition were revealed through the use of a more sensitive behavioral paradigm, suggesting that ERβ plays only a modulatory role in social recognition in mice (Choleris et al., 1998). In a recent study utilizing a paradigm involving anesthetized social stimuli, both male and female ERβKO mice were not impaired in social recognition, confirming that ERβ is not necessary for social recognition in mice (Sanchez-Andrade & Kendrick, 2011). Furthermore, a sex difference in the dependence of social recognition on ERα may exist. Male ERαKO mice, unlike female ERαKO mice, showed normal short-term social memory formation, but like females they were impaired in retaining the memory for longer intervals (Sanchez-Andrade & Kendrick, 2011). Overall, these studies suggest a key role for ERα in acquisition of social recognition in female mice. ERβ, on the other hand, seems to play a smaller modulatory role.

The partial or complete impairment in social recognition displayed by the ERαKO and ERβKO mice has implications for the ethologically relevant predator and parasite recognition and avoidance. ERαKO and ERβKO females and males were impaired in the recognition of, and displayed attenuated aversive analgesic response to, the odors of males infected with a nematode parasite (Kavaliers et al., manuscript in preparation; Kavaliers, Choleris, & Pfaff, 2005). In addition, these ERαKO and ERβKO mice could not discriminate between the odors of novel and familiar infected males and females, and failed to adaptively modify their aversive reactions to them (Kavaliers, Choleris, & Pfaff, 2005). Similarly, the adaptive modulation of male risk taking was also shown to be dependent upon ERα and ERβ. ERαKO male mice failed to show the increase in risk taking (i.e., a reduction in predator odor avoidance) that males usually display in the presence of the odor of a novel estrous female (Kavaliers, Choleris, & Colwell, 2001; Kavaliers et al., 2008). The ERβKO males, instead, although displaying normally enhanced risk taking, failed to modulate their aversive and predator avoidance responses on the basis of prior familiarity with the female (Kavaliers et al., 2008). These studies demonstrate the consequences of inhibited social recognition under evolutionary adaptive contexts.

Estrogen's effects on social recognition may be explained, in part, through its regulation of both OT and OTR production. Estrogens are known to promote the synthesis of OT and OTR mRNA. In fact, OT and OTR mRNA levels fluctuate with the estrous cycle in a manner consistent with fluctuations in circulating levels of estrogen (Ho & Lee, 1992; Sarkar, Frautschy, & Mitsugi, 1992) and are both reduced by ovariectomy. OT production is directly regulated by estrogens in rats (Dellovade, Zhu, & Pfaff, 1999) and the electrical excitability of neurons involved in OT production in the PVN is increased by estrogen administration (Akaishi & Sakuma, 1985).

OT production in the PVN, where ERβ (Mitra et al., 2003) but not ERα is highly expressed, is thought to be modulated by ERβ (Patisaul, Scordalakes, Young, & Rissman, 2003). Accordingly, administration of estrogens to ERβKO male (Nomura et al., 2002) and female mice (Patisaul et al., 2003) cannot induce OT expression in the PVN; however, baseline OT and OT mRNA levels in the PVN are still normal (Patisaul et al., 2003). These baseline

levels of oxytocin may explain why social recognition is only partially impaired in ERβKO mice (Choleris et al., 2006). Furthermore, performance in social discrimination may be enhanced by ERβ-modulated production of OT above baseline levels in WT mice (Choleris et al., 2006).

Estrogens also regulate the density of OTRs and the expression of the OTR gene in the medial amygdala, where, as mentioned earlier, OT/OTR actions (Choleris et al., 2007) mediate social recognition in mice (De Vries, 2008). The estrogenic regulation of OTR is mediated by the highly expressed ERα in the medial amygdala (Mitra et al., 2003) and is necessary for the induction of the OTR (Young, Wang, Donaldson, & Rissman, 1998). Conversely, ERβ is not needed for OTR gene transcription (Patisaul et al., 2003), even though it is also highly expressed in the medial amygdala (Mitra et al., 2003). The dependence of OT's action on ERα but not ERβ in the medial amygdala can explain why the ERαKO mice are completely impaired, while the ERβKO mice are only partially impaired in the social discrimination paradigm (Choleris et al., 2006). Consistently, reduction of ERα expression in the amygdala of female rats with short hairpin RNA selectively impaired social recognition in the habituation/dishabituation paradigm in rats. These females showed no reduction in their investigation response after repeated presentations of a conspecific juvenile and no change in social investigation when the familiar juvenile was replaced with a novel one (Spiteri et al., 2010). Overall, it seems that ERα, possibly through regulation of OT/OTR production in the medial amygdala, is essential to social recognition in mice and rats, while ERβ seems to play a facilitatory role in.

Recently, estrogens have been shown to affect social recognition on a rapid time scale in ovariectomized female mice. In fact, both 17β-estradiol and ER selective agonists could rapidly affect performance in a social recognition paradigm that is completed within 40 min of drug administration. It was shown that very low doses of 17β-estradiol, within physiological levels, were able to improve social recognition (Phan et al., 2010). Furthermore, PPT, an ERα agonist, enhanced social recognition in ovariectomized female mice, while 2,3-bis(4-Hydroxyphenyl)-propionitrile (DPN), an ERβ agonist, slightly impaired social recognition (Phan et al., 2011). Likewise, selective activation of G-protein-coupled estrogen receptor 1 (GPER), an ER capable of initiating rapid cellular signaling events in response to estrogen, was shown to improve social recognition within 40 min of administration of the GPER selective agonist, G-1 (Gabor et al., 2011). The rapid time scale of these effects suggests that estrogens can affect social recognition via nongenomic mechanisms of action. In addition, similar to the results of long term studies, these results support the notion that ERα activity is more important than ERβ activity in promoting social recognition. These rapid effects, however, do not seem to be specific to social memory since 17β-estradiol, the ERα agonist PPT, the ERβ agonist DPN and G-1 were also able to rapidly enhance performance of nonsocial object recognition and spatial learning in the object location paradigm (Gabor et al., 2011; Phan et al., 2010; Phan et al., 2011). Given that both PPT and DPN were able to affect dendritic spine density in regions of the hippocampus within 40 min of administration in ovariectomized female mice (Phan et al., 2011), it may be that estrogens rapidly influence learning through the modulation of hippocampal cell signaling. In fact, estrogens acting in a nongenomic manner, through intracellular and membrane bound ERs, are capable of activating intracellular signaling cascades involved in memory formation and synaptic plasticity, such as the mitogen activated protein kinase (MAPK) dependent pathway (Thomas & Huganir, 2004). In this regard, recently it has been shown that intrahippocampal delivery of 17β-estradiol rapidly improved both social recognition and object placement learning in mice (Phan et al., 2011) suggesting the involvement of the hippocampus in the effects of estrogens in these learning paradigms.

Androgens and Social Recognition

Androgens are also involved in the regulation of social recognition. Gonadally intact male rats show habituation 30–60 min after initial exposure to a social stimulus. Female and castrated male rats instead show a significant habituation response 2–3 hr after first exposure (Bluthe, Gheusi, & Dantzer, 1993; Thor et al., 1982). Thus, it seems that gonadally intact males are relatively less capable of recognizing familiar conspecifics. However, castrated males do show temporary impairments in social recognition memory within the first week following surgery, but by 2–3 weeks postoperation social recognition ability is fully recovered (Bluthe & Dantzer, 1990; Bluthe & Dantzer, 1993; Bluthe et al., 1993). Conflictingly, social recognition in castrated rats was not different from that of gonadally intact rats when tested every other day after surgery (Bluthe & Dantzer, 1990; Bluthe & Dantzer, 1993). Evidence of social recognition impairment in castrated male rats was described in a study that compared gonadally intact rats with castrated rats in their response to repeated exposure of an individual rat or its odor cues (soiled bedding, urine). Ten minutes after social exposure, gonadally intact rats showed a significant decline in social investigation to both an individual rat and its odor cues, while castrated rats showed reduced investigation of only the same individual stimulus rat, and not of the odor cues, of either the same or a different stimulus rat (Sawyer, Hengehold, & Perez, 1984). Overall, these studies demonstrate the involvement of androgens in social recognition. However, the effects of castration range from improving to impairing depending on the timing of testing after castration (Bluthe & Dantzer, 1990) and the number of times that the rats were tested after castration (Bluthe et al., 1993).

It is unlikely that the androgen receptor (AR) alone mediates effects through developmental means, since daily prenatal exposure with an AR antagonist, flutamide, had no effect on social recognition in male rats (Axelson, Smith, & Duarte, 1999). Moreover, results of several studies have supported the notion that effects of testosterone on social recognition are in fact also regulated by estrogenic mechanisms. Social recognition in the habituation/dishabituation paradigm was impaired in male mice with a mutation in the *cyp19* gene that codes for aromatase, the enzyme responsible for converting testosterone to estradiol through aromatization (Pierman et al., 2008). In addition, it seems that the impairment seen in aromatase knockout (ArKO) male mice was because of activational and not organizational effects of the gene KO, since adult treatment with a combination of estradiol and dihydrotestosterone, two testosterone metabolites, restores social recognition (Pierman et al., 2008). Furthermore, ArKO male mice were impaired in social recognition, even though they have increased testosterone relative to WT males. (Fisher, Graves, Parlow, & Simpson, 1998). Thus, it could be that either

testosterone-AR action impairs social recognition or that estradiol has an important role in social recognition for male mice. Further investigation into testosterone-AR and its relationship to estrogens in regards to social recognition are needed to clarify these mechanisms in both rats and mice.

Because AVP is known to be regulated by testosterone (De Vries, Buijs, & Sluiter, 1984; Szot & Dorsa, 1993; Wang, Bullock, & Devries, 1993), and male rat brains show higher expression of AVP than female brains (De Vries et al., 2002; Mayes, Watts, McQueen, Fink, & Charlton, 1988), it is not surprising that the effects of androgens on social recognition could be mediated by AVP in males. The LS, the region of the brain that is essential for social recognition in males (Appenrodt et al., 2002; Popik & van Ree, 1992), receives projections from brain areas containing testosterone dependent AVP neurons in rats, such as the BNST and the medial amygdala (e.g., Everts, De Ruiter, & Koolhaas, 1997). In male rats, castration reduces AVP expression in several limbic brain areas in a manner that is reversible by testosterone (Zhou, Blaustein, & Devries, 1994). The intact social recognition of female rats and castrated male rats is not dependent upon AVP, as it cannot be affected by the administration of either AVP or AVP antagonists (Bluthe et al., 1990). Furthermore, dependence of social recognition on AVP in castrated rats, but not in females, can be rescued by treatment with testosterone (Bluthe et al., 1990; Wang et al., 1993). These results were comparable to those found in mice (Bluthe et al., 1993). Overall, it appears that social recognition in male rats and mice is mediated by AVP in a testosterone (and estrogen) dependent manner. However, there is evidence that the regulatory effects of testosterone on AVP production may be, at least in part, through its conversion into estrogen, since treatment with estradiol, but not dihydrotestosterone (Han & De Vries, 2003), reversed the reduction of AVP levels seen in male castrated rats (Brot, De Vries, & Dorsa, 1993; De Vries, Wang, Bullock, & Numan, 1994). Moreover, male ArKO mice show reduced levels of AVP immunoreactivity in the LS, medial amygdala, BNST and the supraoptic nucleus (Pierman et al., 2008; Plumari et al., 2002). In addition, studies using male ERαKO mice suggest that ERα, along with ARs, promote AVP expression in the limbic system (Scordalakes & Rissman, 2004). However, opposite to their effect on OT, estrogens reduce AVP synthesis in the PVN, (Nomura et al., 2002). Treatment with estrogens in ERβKO mice did not result in the reduction of AVP in the PVN suggesting a role for ERβ in AVP synthesis that is opposite to that of OT in the PVN in mice (Nomura et al., 2002). Overall, it seems that androgens, especially in males, play a role in social recognition indirectly, possibly by regulating AVP and estrogen systems. However, the exact mechanism is still unknown and is yet to be elucidated in both rats and mice.

Conclusions and Implications for Other Social Cognitive Behavior

We have reviewed here various studies with rats and mice whose findings support the idea that social recognition is regulated by a complex sex-dependent action of OT and AVP. It seems that estrogens facilitate social recognition by promoting OT action through specific activation of ERs. Males seem to be more reliant than females on AVP, particularly V1aR, for social recognition in an androgen-dependent manner, even if the system may be ultimately mediated by estrogenic mechanisms (Scordalakes & Rissman, 2004). The specific brain areas involved in social recognition are also, to some extent, sexually dimorphic, with the lateral septum being important for social recognition in males (Appenrodt et al., 2002; Everts & Koolhaas, 1999; Landgraf et al., 1995) and the medial amygdala being essential to both males and females (Choleris et al., 2007; Ferguson et al., 2001). In addition, recent studies suggest that estrogens and their receptors may also mediate social recognition within a very rapid time frame. These rapid effects support the important role for ERα in social recognition and also integrate the effects of the more recently described membrane-bound GPER. The specific brain areas and mechanisms of these rapid effects on learning are only beginning to be investigated, and it seems that they may involve nongenomic estrogenic actions in the hippocampus (Phan et al., 2011; Zhao & Brinton, 2007) and possibly other brain areas, such as the medial amygdala, that are required for social recognition (Spiteri et al., 2010). Whether or not these rapid effects also involve nongenomic OT and/or AVP mechanisms (e.g., by influencing the release of the peptides or the trafficking of their receptor) is currently unknown and deserves further investigations.

It is also becoming evident that the underlying neuroendocrine systems regulating social recognition are related to those of other social–cognitive behaviors, such as social learning. For instance, OT was shown to be involved in female mate choice copying, a type of social learning (Kavaliers, Choleris, Agmo, Braun, Colwell, Muglia, Ogawa, & Pfaff, 2006). Furthermore, OT, AVP, and estrogens are all involved in the social transmission of food preferences (STFP), a specifically social and biologically relevant task in which an animal learns to prefer the food consumed by a conspecific (reviewed in Choleris et al., 2009). Exogenous administration of OT and AVP generally improves the STFP (Bunsey & Strupp, 1990; Popik & van Ree, 1993; Strupp, Bunsey, Bertsche, Levitsky, & Kesler, 1990), though under some conditions (i.e., when the task is easier to perform) AVP impairs it (Bunsey & Strupp, 1990; Strupp et al., 1990). In addition, long-term activation of ERα impaired, while that of ERβ prolonged the socially acquired food preference (Clipperton et al., 2008). Through careful manipulations of the timing of treatment, it was further shown that acute long-term activation of ERα blocks all phases of memory processing (acquisition, consolidation, and retrieval). ERβ, instead, seems to be mostly involved in acquisition and consolidation processes via different mechanisms, such that ERβ agonist administration results in enhanced acquisition, but impaired consolidation of the socially acquired memory (Clipperton-Allen et al., 2011). Although it is apparent that both social learning and social recognition are under estrogenic regulation, it seems that the role of the ERs differ; while inhibits social learning, ERα enhances social recognition; ERβ instead, prolongs social learning and plays a less important role in social recognition than ERα (Clipperton et al., 2008; Clipperton-Allen, Almey, Melichercik, Allen, & Choleris, 2011). This demonstrates the sheer complexity of the systems governing social behaviors and stresses the importance of investigating multiple aspects of social cognition in studies on the neurobiology of social behavior.

Understanding the proximate mechanisms of social recognition and other social information processing in naturalistic and evolutionarily relevant contexts, such as those involving food choices (Clipperton et al., 2008), mate choices, reproduction and risk

taking (Kavaliers et al., 2006; 2008, 2006; 2008), and the recognition and avoidance of parasitized conspecifics and predators (Kavaliers et al., 2005), can help us elucidate social behavior as a whole. Understanding the neuroendocrine systems regulating social cognition can, in turn, also offer insights into the development and regulation of abnormal social disorders that are highly sexually dimorphic, such as autism spectrum disorder (Carter et al., 2007).

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