CHAPTER 12

NEUROBIOLOGY OF SOCIABILITY

Heather K. Caldwell

Laboratory of Neuroendocrinology and Behavior, Department of Biological Sciences and School of Biomedical Sciences, Kent State University, Ohio, USA
Email: hcaldwel@kent.edu

Abstract: Sociability consists of behaviors that bring animals together and those that keep animals apart. Remarkably, while the neural circuitry that regulates these two "faces" of sociability differ from one another, two neurohormones, oxytocin (Oxt) and vasopressin (Avp), have been consistently implicated in the regulation of both. In this chapter the the structure and function of the Oxt and Avp systems, the ways in which affiliative and aggressive behavior are studied and the roles of Oxt and Avp in the regulation of sociability will be briefly reviewed. Finally, work implicating Oxt and Avp in sociability in humans, with a focus on neuropsychiatric disorders will be highlighted.

INTRODUCTION

Sociability is the tendency to seek social interactions. Navigating a social environment is not easy; for instance, the ability to discriminate a male from a female will impact the decision to fight versus mate. Yet, while the importance of engaging in normal social behavior seems obvious, our understandings of the neurobiological mechanisms underlying sociability are just now coming to light. Interestingly, it is the lack of sociability found in several neuropsychiatric disorders, such as autism and schizophrenia that has been the impetus for much of the research in this area.[1,2] To date, two neuropeptides, oxytocin (Oxt) and vasopressin (Avp), have been consistently linked with the neural regulation of sociability. With recent developments in behavioral tests to model aspects of sociability, the use of comparative studies, as well as the use of viral vectors and transgenic animals, including knockout mice, our understanding of the neural underpinnings of sociability is improving, as is our understanding of the contributions of Oxt and Avp. This chapter will

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focus on mammals and will review the behavioral components of sociability, describe the ways in which sociability is experimentally assessed, explore the contributions of Oxt and Avp to sociability and delve into some of the data on the neurobiology of altered sociability in human neuropsychiatric disorders.

SOCIABILITY IN CONTEXT

Social behavior is highly complex and varied, with some animals living in groups with complicated social structures while others are solitary and only engage in social interactions intermittently. Some of the questions researchers in this field have focused on include: Why does an animal engage in a social behavior in a specific context? What social or environment cues are required for a social exchange to occur? How does the brain regulate social interactions?

Sociability can be separated into two categories: (1) behaviors that bring animals together, such as affiliative, parental, or copulatory behaviors and (2) behaviors that separate animals, such as aggressive behaviors. This chapter will focus on the neural regulation of affiliative and aggressive behaviors; for reviews on neural regulation of parental and copulatory behaviors, please see Hammock and Young,[3] Lim and Young,[4] McCarthy and colleagues.[5]

MAJOR NEUROHORMONES IMPORTANT TO THE REGULATION OF SOCIABILITY

The first biochemicals implicated in the regulation of sociability were the gonadal steroids.[6] This hypothesis stemmed from research demonstrating that there were changes in sociability, particularly aggressive behavior, as a result of androgen manipulation, (e.g., castration or hormone replacement). There are also several species, particularly seasonal breeders, which continue to have elevated levels of aggressive behavior despite dramatic reductions in gonadal steroids.[7-11] It seems that in many species gonadal steroids may be necessary, but not sufficient, to alter sociability. Rather, the neuropeptides Oxt and Avp have been implicated in the neural regulation of sociability and specifically differences in their receptor distributions appear to be of particular importance.

The Nonapeptides: Oxytocin and Vasopressin

Oxt and Avp are both nine amino acid neuropeptides (i.e., nonapeptides) synthesized primarily in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus. Their genes sit in opposite transcriptional orientations on the chromosome as the result of the duplication of an ancestral vasotocin gene.[12,13] Both genes are composed of three exons, differ from one another by only two amino acids and are synthesized as part of a larger precursor preprohormone.[14] Since they are so structurally similar, Oxt and Avp are considered "sister" hormones though their actions both peripherally and centrally differ significantly from one another. Interestingly, Oxt and Avp are linked to several aspects of sociability and their actions appear to be fairly conserved across mammalian species.[15-21]

Oxytocin

Some of the early work on Oxt characterized its peripheral actions on the regulation of uterine contraction and milk ejection.[22,23] It is its synthesis in larger, magnocellular neurons of the PVN and SON, which project to the posterior pituitary that mediate the aforementioned actions. Oxt synthesized in the smaller, parvocellular, neurons of the PVN project centrally and mediate many of the central actions of Oxt. In mice and various vole species there have also been reports of Oxt neurons outside of the PVN.[24-26] For example, in female prairie voles (*Microtus ochrogaster*) Oxt immunoreactive (Oxt-ir) fibers that originate from both the PVN and SON have been found to innervate the nucleus accumbens (NAcc); the significance of which will be discussed later.[27]

Thus far only a single Oxt receptor (Oxtr) has been identified and it is thought to transduce all of the actions of Oxt.[28,29] The Oxtr is a member of the seven transmembrane G-protein-coupled receptor family; it is also structurally similar to the Avp receptors.[30] Identification of Oxtr expression was initially determined with receptor autoradiography using a potent ^{125}I-labeled antagonist. In rats and mice, Oxtr binding is found in several areas, including the hippocampal formation, lateral septum (LS), central amygdala (CeA), olfactory tubercle, nucleus accumbens shell, dorsal caudate-putamen, bed nucleus of the stria terminalis (BNST), medial amygdala (MeA) and ventromedial hypothalamus (VMH).[31-33]

Vasopressin

Avp's peripheral actions include the regulation of salt and water balance. Avp made in the magnocellular neurons of the PVN and SON is transported to the posterior pituitary and its release from the posterior pituitary regulates most of its peripheral actions. Centrally, Avp is also expressed in the suprachiasmiatic nucleus (SCN), BNST and MeA.[34] There are also reports of Avp immunoreactive (Avp-ir) neurons in the medial septum, LS, vertical limb of the nucleus of the diagonal band of Broca and the locus coeruleus.[35] Between the projections provided by the parvocellular vasopressinergic neurons of the PVN and the aforementioned nuclei, Avp fibers are extensive within the central nervous system.[36-39]

Avp receptors can be divided into two classes: Avp1 and Avp2 receptors (Avpr1 and Avpr2, respectively), both of which are seven transmembrane G-protein-coupled receptors that are similar in structure to the Oxtr. There are two subtypes of the Avpr1: The Avpr1a and the Avpr1b. Peripherally, the Avpr1a mediates the effects of Avp on vasoconstriction and can be found in the liver, kidney, platelets and smooth muscle.[40,41] Centrally, the Avpr1a is found in a variety of brain nuclei.[42-45] The Avpr1b was originally described in the anterior pituitary, where is prominent on the corticotrophes; though, it can also be found in the brain.[46,47] In rats, the Avpr1b has been localized to areas such as the olfactory bulb, piriform cortical layer II, LS, cerebral cortex, hippocampus, PVN, SCN, cerebellum and red nucleus,[47-51] but initial immunohistochemical and in situ hybridization histochemistry (ISHH) studies may have used antibodies and probes that lacked specificity.[52] In rats and mice however, the Avpr1b appears to be more discretely localized with prominent expression in the hippocampal field CA2 pyramidal neurons.[52] The Avpr2 is found in the periphery and is primarily expressed in the kidney; it has not been localized to the brain. Its role in the kidney is to transduce the antidiuretic effects of Avp within the renal collecting ducts.[53]

SOCIAL BEHAVIORS

On the surface, affiliative and aggressive behaviors appear to represent opposite ends of a behavioral spectrum and in fact, many of the neurotransmitters/neurohomones that regulate affiliative and aggressive behaviors are the same. However, the neuroanatomical substrates on which they act differ, suggesting that the neural circuits that underlie affiliative and aggressive behaviors differ significantly from one another. In this section, the defining features of affiliative and aggressive behaviors, how they are experimentally tested and their neural regulation will be explored.

Affiliative Behavior

Affiliative behaviors are those that include social bonding between individuals, including bonds between mates and parents with their offspring. From an evolutionary, perspective social bonds serve to reduce stress and anxiety by increasing security.[54,55] As most mammalian species are social, the formation of social bonds aids in holding groups or pairs of individuals together.

Social bonds have been studied extensively in primates and in some instances have been shown to increase evolutionary fitness.[56] For example, in a group of free-ranging baboons, females that have strong social bonds with one another live longer than those who have weaker social bonds.[57] In other mammals the direct effect of social bonding on fitness has been less studied, though a recent study in feral horses did find that in unrelated females, social bonding improved reproductive success.[58] So, it may be that for many species, social bonding has a direct benefit on fitness and that it simply has not been adequately studied across species.

The proximate cause, i.e., the neural regulation, of social bonds between male and female mammals has only been studied extensively in one species, the prairie vole.[4,18,54,59,60] Specifically, prairie voles have been used to examine the formation of the "pair bond", which is the social bond formed between males and females of a species that often implies social monogamy.[61]

The Pair Bond

Prairie voles live in extended family groups and are considered a socially monogamous species.[62] The pair bond is defined as a preference for contact with a familiar sexual partner, selective aggression towards unfamiliar conspecifics, biparental care, socially regulated reproduction and incest avoidance.[61,62] The formation of a pair bond is experimentally tested in the laboratory using a partner-preference test.[63] In this behavioral test, a male and female are paired and allowed to cohabitate. To test for the pair bond, one of the "partner" individuals is tethered to one side of a three-chambered apparatus. A novel "stranger" animal is tethered to the opposing chamber. The subject animal is permitted to explore the three chambers freely and the amount of time the subject animal spends in proximity to, or huddling with, the "partner" versus "stranger" animal is recorded over a 3-hour testing period. If the subject spends twice as much time with the "partner" animal then it is said to have formed a pair bond with that individual.[61,62,64,65]

Due to the diversity in social structures within the genus *Microtus*, comparative studies between vole species has provided significant insight into the neural regulation

of social bonding. By comparing the neurochemistry of monogamous vole species, such as the prairie or pine vole (*Microtus pinetorum*), to nonmonogamous voles, such as the montane (*Microtus montanus*) or meadow (*Microtus pennsylvanicus*) voles, scientists have had the opportunity to explore how variations in neurochemistry between highly related species can result in significant differences in social behavior. Differences in the Oxt and Avp systems between vole species has been found to contribute to their social organization.[18,60]

While there are not marked differences in Oxt and Avp immunopositive cells, or their projections, between species, there are changes in the distribution of the receptors for Oxt and Avp. Relative to nonmonogamous voles, monogamous voles have higher densities of Oxtr, as measured using Oxtr autoradiography and ISHH, in the NAcc, prefrontal cortex (PFC) and the BNST. Promiscuous voles, on the other hand, have higher Oxtr density in the LS, VMH and the cortical nucleus of the amygdala.[66-68] Evidence that the differences in the distribution of the Oxtr between species might be behaviorally meaningful comes primarily from pharmacological studies.

In female prairie voles, central infusion of an Oxtr antagonist blocks the formation of the pair bond but has no effect on sexual behavior, whereas central infusion of Oxt facilitates the pair bond in the absence of mating.[65,69,70] In the aforementioned studies the infusions were intracerebroventricular (icv), however manipulation of Oxtr signaling, using Oxtr antagonists within the NAcc, blocks formation of a partner preference following mating (Fig. 1).[71,72] This finding is supported by a recent study in which Oxtr overexpressed in the NAcc of adult female prairie voles was found to accelerate the formation of partner preference. Interestingly, the same result was not found when the Oxtr was overexpressed in the nonmonogamous meadow vole, suggesting that in a nonmonogamous species Oxtr expression within the NAcc is not sufficient to promote pair bond formation.[73]

There are also differences in the distribution of the Avpr1a between vole species. Prairie voles have a higher density of Avpr1a, as measured using receptor autoradiography and ISHH, within the MeA, accessory olfactory bulb, diagonal band, thalamus, ventral pallidum (VP) and BNST compared to montane voles.[74,75] Montane voles, on the other hand, have a higher density of Avpr1a in the medial PFC and the LS.[68,75] These differing "patterns" of Avpr1a distribution have been suggested to underlie differences in social organization between monogamous and nonmonogamous vole species. This hypothesis has been confirmed, in part, by data in pine voles and meadow voles which suggest similar, social structure-specific distributions of Avpr1a between these species.[75] Further support for this hypothesis comes from pharmacological manipulations of the Avpr1a in prairie voles. When an Avp antagonist is injected icv prior to mating, the formation of a partner preference is inhibited. Conversely, Avp infusion facilitates the formation of the partner preference.[70,76] Some of the more interesting data that supports a role for the differential distribution of the Avpr1a in the formation of social bonds comes from a study in which the prairie vole Avpr1a gene was overexpressed in the ventral forebrain of meadow voles, resulting in increases in the amount of time meadow voles spent huddled with their partners compared to controls.[77]

It has been suggested that the differences in Avpr1a distribution between species are due to changes in the regulatory region upstream of the Avpr1a promoter.[78-80] This idea is based on work demonstrating that changes in Avpr1a density within and between species can alter social behavior.[77,81,82] Hammock and colleagues[83,84] suggest

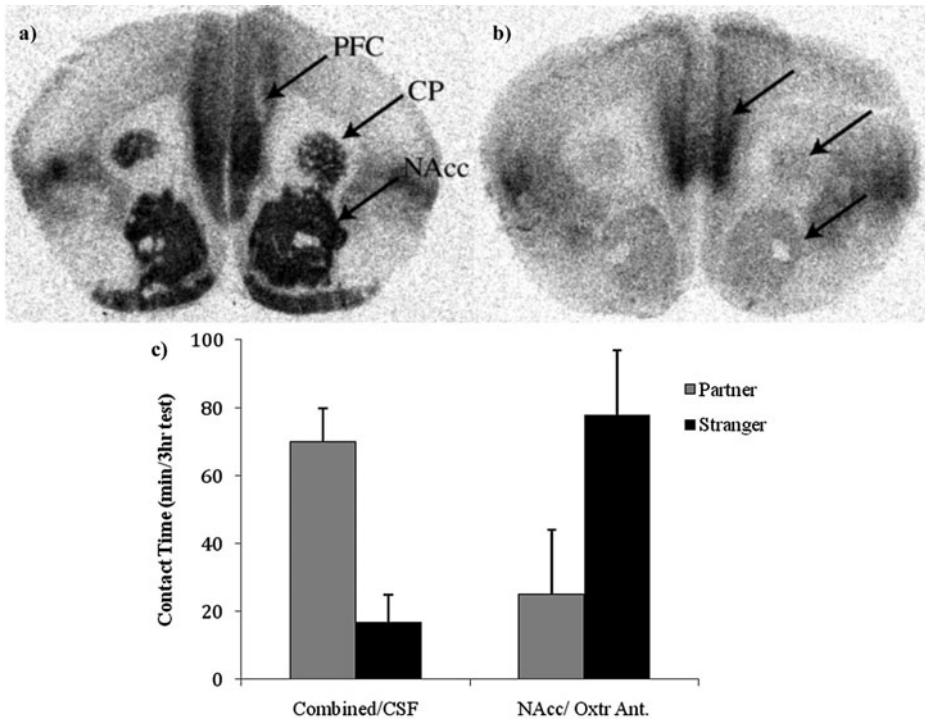

Figure 1. In female prairie voles, oxytocin receptors (Oxtr) in the nucleus acumbens (NAcc) are thought be important for the formation of partner preference. Autoradiograms illustrating Oxtr distribution between monogamous female prairie voles (A) and nonmonogamous female meadow voles (B) demonstrate that female prairie voles have increased Oxtr binding in the prefrontal cortex (PFC), the caudate putamen (CP) and the NAcc compared to female meadow voles. Further, female prairie voles given a selective Oxtr antagonist into the NAcc prior to and 12 hours into a 24 hour cohabitation period do not form a partner preference compared to females that received cerebral spinal fluid (CSF) into the PFC, CP and NAcc at the same time points (i.e., combined). (C). (A) and (B) were adapted from Hammock and Young. J Phil Trans R Soc B 2006; 361:2187-2198,[3] ©2006 with permission from The Royal Society. (C) was adapted from Young et al. Horm Behav 2001; 40:133-138,[72] ©2001 with permission from Elsevier.

that the presence or absence of a microsatellite sequence (i.e., simple sequence repeats with nonrepetitive elements) in the 5′ cis-regulatory region of the Avpr1a gene could be responsible for differences in Avpr1a density. To test this, two breeding lines of prairie voles were generated that had differing lengths of microsatellite sequence in the 5′ cis-regulatory region of the Avpr1a gene. The two breeding lines showed regional differences in the density of the Avpr1a and the breeding line with the longer microsatellite sequence tending to show more partner preference than the breeding line with the shorter microsatellite sequence.[83] However, in a study that examined individual differences in Avpr1a expression in prairie voles housed in a semi-natural setting, Avpr1a expression in the VP or LS was found to not be predictive of social or sexual fidelity. Rather, differences in Avpr1a expression in brain areas associated with spatial memory were correlated with social and sexual fidelity.[85] Further, differences in microsatellite length in field tests of prairie voles, while associated with Avpr1a density in brain areas important for pair bond formation, are not associated with differences in measures of

monogamous behavior and reproductive success.[86] Taken together, these data suggest that there are a variety of social and neurobiological factors that likely contribute to the formation of the partner preference and that changes in single gene are not sufficient to determine whether an animal is monogamous or polygamous.

Aggressive Behavior

Aggression is used by a variety of animals to develop and maintain social hierarchies, gain access to mates, protect young and defend territories. The ability to display aggression in the correct social context is critical for the survival and reproductive success of many species. Males are typically more aggressive than females, however, during pregnancy and in the postpartum period, there is often a rise in female aggression.[87,88] Our understanding of the neural regulation of aggressive behavior is fairly limited in primates, but in rodents, pharmacological tools coupled with transgenic mouse models have substantially contributed to our understanding of the neural regulation of aggression.

In rodents, the most common assessment of aggression, specifically offensive aggression, uses the resident-intruder test. Subject "resident" animals are singly housed for several weeks prior to testing; in mice this results in an increase in baseline aggression due to isolation-induced aggression. An "intruder" animal, often smaller and group housed, is then placed into the cage of the resident animal. The latency to the onset of aggression as well as the frequency and duration of aggression are common behavioral measures. To test maternal aggression a similar test is employed, only the "resident" is a postpartum female with her pups in or removed from the cage.

The role of Oxt in the neural regulation of aggression has not been examined in much depth. Though, it does appear that in females Oxt reduces nonmaternal aggression in some species and facilitates maternal aggression in others. In female Syrian hamsters (*Mesocricetus auratus*), for instance, which are more aggressive than males of the species, there is evidence that a microinjection of Oxt into the medial preoptic area-anterior hypothalamus (MPOA-AH) reduces aggression directed toward a female intruder,[89] but microinjections of Oxt, as well as Oxt antagonists, into the amygdala facilitate maternal aggression.[90,91] Female prairie voles that receive Oxt icv have decreases in male-directed aggression[92] and in rats, displays of maternal aggression can be facilitated by infusing Oxt into the amygdala[91] and reduced by lesioning or infusing Oxt antisense oligonucleotides into the PVN.[93,94] While there are mice in which Oxt and the Oxtr have been genetically disrupted, $Oxt^{-/-}$ and $Oxtr^{-/-}$ mice, respectively there are no reports of altered maternal aggression in these animals.[95,96] Overall, the actions of Oxt in the regulation of aggression in females appears to be context specific and possibly species specific.

There have been very few reports supporting a role for Oxt in the regulation of aggression in males. Studies in $Oxt^{-/-}$ mice are conflicting, with one group reporting increases in aggressive behavior[97] and another group reporting decreases in aggressive behavior.[98,99] It should be noted, though, that the $Oxt^{-/-}$ mice tested were generated by two different groups and that the increases in aggressive behavior were only found in mice that were the offspring of null mutant parents; suggesting that Oxt exposure in the prenatal environment may be important to normal displays of aggression. This possibility is supported by a report of heightened aggression in $Oxtr^{-/-}$ male mice compared to controls when tested in a resident-intruder behavioral test.[96]

Much of the work implicating Avp in the neural regulation of aggression has been completed in Syrian hamsters. As Syrian hamsters are a solitary species, they readily display aggression towards conspecifics. Further, they engage in a stereotypic type of scent marking behavior, referred to as flank marking, that is expressed at higher levels in socially dominant animals.[100] Ferris and colleagues made the serendipitous discovery that Avp injected into the MPOA-AH results in a dose-dependent increase in flank marking behavior.[101] This finding was one of the first to demonstrate that microinjection of a single neuropeptide into a specific brain region could induce a complex behavior. Avp injected into the anterior hypothalamus (AH) or ventral lateral hypothalamus (VLH) of Syrian hamsters has been found to facilitate aggressive behavior.[7,102,103] Conversely, Avp antagonists and more specifically Avpr1a antagonists, injected into the AH inhibit aggression.[102] The Avpr1b may also be important to the modulation of aggressive behavior in hamsters, as treatment with an oral Avpr1b antagonist results in decreases in aggressive behavior compared to controls.[104] It has been suggested that the neural circuit that regulates aggression in Syrian hamsters includes the AH, which has reciprocal connections with the VLH, the MeA and the BNST.[105,106]

Syrian hamsters exposed to anabolic-androgenic steroids during adolescence for at least 14 days display increased aggression in adulthood. They also have increases in Avpr-ir within the AH and injections of an Avpr1a antagonist in the AH reduces the intensity but not the onset of aggression.[107-110] There are also reports of changes in social status affecting the Avp system in hamsters. Injections of an Avp antagonist into the MPOA-AH of a dominant hamster can transiently reverse dominant/subordinate relationships, as measured by flank marking.[111] Subordinate hamsters have fewer Avp-ir cell bodies in the nucleus circularis, a structure that is found within the AH, compared to dominant hamsters.[112] In hamsters that are repeatedly defeated, there are coincident decreases in Avpr1a receptor binding within lateral portions of the VMH.[113] Similarly, in hamsters that are singly housed for several weeks and not allowed to interact with other animals, there are increases in Avpr1a binding in the AH, PVN and lateral hypothalamus, whereas socially experienced hamsters have increased Avpr1a binding within the CeA.[114] Even when Avp is used to facilitate aggression, social isolation for some period of time seems to be required.[7,106] These data suggest that, at least in hamsters, the role of Avp in the regulation of aggression can be altered by social experience.

The modulation of aggression in rats and mice is due in part to gonadal steroid-dependent Avp projections from the BNST and the MeA to the LS.[115-117] With the LS likely regulating the emotional aspects of aggression.[118,119] Injections of Avp into the LS of rats and prairie voles can facilitate agonistic behavior.[76,120,121] In sexually naïve males, Avp injected into the AH, or overexpression of the prairie vole Avpr1a within the AH, results in increases in selective aggression (i.e., aggression directed towards novel male or female animals).[122] In mice selectively bred for either a long attack latency (LAL) or short attack latency (SAL), there is evidence of changes in Avp neurochemistry. SAL mice have fewer Avp-ir neurons in the BNST and fewer Avp-ir fibers in the LS compared to LAL mice suggesting that, within a species, less Avp within the LS may be associated with increased aggression.[123] However, monogamous California mice (*Peromyscus californicus*) have shorter attack latencies and increased Avp-ir in the BNST and LS compared the polygamous, white-footed mice (*Peromyscus leuopus*).[124] Interestingly, when California mice are cross-fostered to white-footed mice dams, they are less aggressive in adulthood than those reared by the same species and they have

less Avp-ir in the BNST and SON compared to controls.[125] The data in Peromyscus mice suggest that, similar to what has been found in hamsters, changes in the environment, in this case changes in the early postnatal period, are able to alter the Avp neurocircuity and subsequent behavior.

When mice with a genetic disruption of their *Avpr1a* were engineered, it was thought that they would provide some valuable insight into the role of the Avpr1a in the regulation of aggression. Surprisingly, Avpr1a knockout mice do not differ from wildtype controls in measures of aggression.[126] It may be that the lack of aggressive phenotype in these mice is due to developmental compensation. Mice with a disruption of the *Avpr1b* (Avpr1b$^{-/-}$ mice), on the other hand, have implicated the *Avpr1b* in the regulation of aggressive behavior. Avpr1b$^{-/-}$ mice have marked reductions of forms of "social" aggression (i.e., those forms of aggression that require the animal to interact with a conspecific), such as those measured in resident-intruder, neutral arena and maternal aggression tests and no change in predatory aggression.[127-129] When attacked, Avpr1b$^{-/-}$ mice will defend themselves but will initiate fewer "retaliatory" attacks compared to wildtype controls.[128] Even Avpr1b$^{-/-}$ mice that are crossed with a more outbred substrain of mice, *Mus musculus castaneous*, continue to have reduced aggression (Fig. 2).[130] Since the distribution of the Avpr1b in the mouse brain is fairly restricted, with prominence in the CA2 field of the hippocampus, it has been proposed that it may be important to the formation or recall of memories that have an accessory olfactory-based component.[52,127]

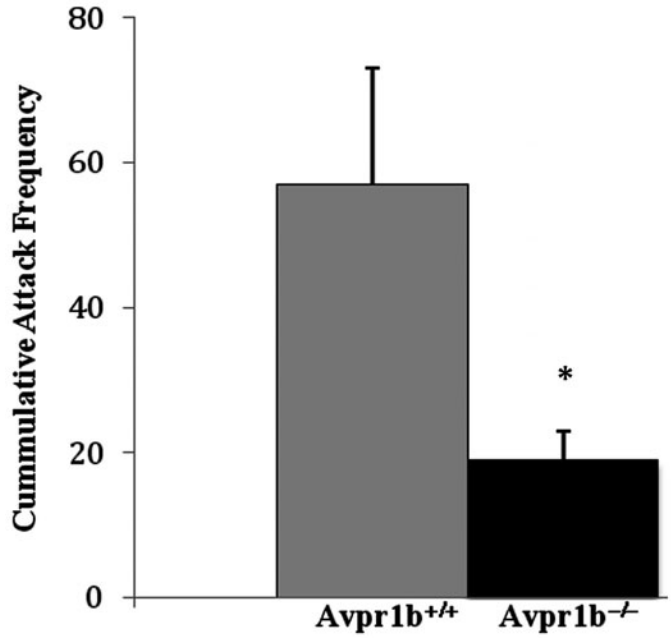

Figure 2. Even when crossed with *Mus musculus cantaneus*, male Avpr1b knockout mice (Avpr1b$^{-/-}$) have reduced aggression compared to wildtype (Avpr1b$^{+/+}$) controls; as measured by fewer attacks in a resident-intruder behavioral test. Adapted from Caldwell and Young. Physiol Behav 2009; 97:131-134,[130] ©2009 with permission from Elsevier.)

SOCIABILITY IN HUMANS

In humans there is evidence that Oxt promotes prosocial behavior. The study of prosocial behavior in humans includes testing procedures designed to measure trust, the ability to read facial expressions and the memory for socially salient information, such as faces. In most of the studies in humans, Oxt has been administered intranasally, as Oxt is thought to be able to cross the blood brain barrier using this route of delivery.[131] Intranasal administration of Oxt results in an increase in trust in humans, as measured by an individual's willingness to accept social risk during a social interaction.[132] Further, when intranasal Oxt treatment is coupled with functional magnetic resonance imaging, there is a reduction in activity in areas of the brain associated with processing fearful stimuli, such as the amygdala and some areas of the midbrain and reward feedback, such as the striatum. In individuals administered Oxt intranasally, betrayal of trust results in no change in trust behavior, whereas placebo controls decrease their trust in response to betrayal.[133] These data suggest that Oxt acting as an anxiolytic and stress-reducer is allowing for higher levels of sociability. There is also evidence that intranasal Oxt improves the ability to infer another individual's mental state, improves facial recognition memory and alters the processing of faces.[134-138]

The role of vasopressin in the regulation of social behavior in humans has not been studied as extensively as Oxt, though it is often associated with antisocial rather than prosocial behavior. In males, Avp administered intranasally results in increases in electromyogram (EMG) activity to socially neutral facial expressions. This suggests that Avp acts to bias an individual to perceive a neutral stimulus as an aggressive or threatening stimulus.[139] When administered to females, Avp decreases EMG responses to happy and angry faces, suggesting that in females, Avp acts to increase the perception of friendliness.[140] The researchers that conducted the aforementioned work suggest that the differential actions of Avp between men and women reflect differences in social strategies during socially stressful interactions.

Neuropsychiatric Disorders

Oxt and Avp have also been implicated in a variety of neuropsychiatric disorders, particularly those that are characterized by alterations in social interactions or heightened aggression, such as: Autism spectrum disorders (ASD), personality disorder and schizophrenia. In this section the contributions of Oxt and Avp to neuropsychiatric disorders will be briefly reviewed.

Autism Spectrum Disorders

ASD are characterized by repetitive behaviors, communication difficulties and abnormal sociability.[141,142] One of the reasons Oxt has been suggested to contribute to ASD is that in mice that lack Oxt, or Oxtr, there are behavioral deficits that are consistent with some of the symptoms of ASD.[95,143-149] Evidence that Oxt may have a role in ASD comes from several sources. There are reports of lower Oxt in the CSF of autistic children and reduced Oxt is correlated with impairments in social functioning.[150] There are also increases in the amount of an Oxt prohormone in the blood of autistic children, which is indicative of incomplete processing of Oxt into its biologically active form.[151] Oxt treatment in adults with ASD results in the reduction

of repetitive behaviors and improvements in emotional recognition.[152,153] Some genetic and epigenetic links between the Oxt system and ASD have also started to emerge. There are data in the Chinese Han population, Finnish families, Caucasian children and in individuals with "high-functioning" ASD suggesting that portions of the Oxtr gene may contain susceptibility loci for ASD.[154-157] Epigenetic modifications of the Oxtr gene have also been reported, with hypermethylation of the Oxtr promoter found in autistic subjects and subsequent reductions in Oxtr mRNA.[158] Though the sample size in the aforementioned study is small, the data are provocative and will likely facilitate more research in this area.

Data implicating Avp in the etiology of ASD are sparse, but there have been studies suggesting that polymorphisms of the Avpr1a may contribute to ASD.[159-161] Further, two of the polymorphisms, RS3 and RS1, have been linked to differential activation in the amygdala,[162] providing a possible neural substrate with which the Avp system may interact to mediate a genetic risk for ASD.

Personality Disorder

Personality disorder is characterized by a disconnect between an individual's behavior and cultural norms. Those diagnosed with personality disorder have impairments in at least two of the following areas: (1) cognition, (2) affectivity, (3) interpersonal functioning and (4) impulse control.[163] To date, only one study has examined changes in Oxt between individuals diagnosed with a personality disorder and healthy controls. This study found that while having a personality disorder was not correlated with cerebral spinal fluid Oxt, a life history of suicidal behavior was inversely correlated with Oxt.[164] The authors suggest that these data are consistent with the previous work in animal models which suggest that Oxt reduces aggression.[89,92-94]

Since individuals with a personality disorder are often more impulsive, which can result in increased aggression, it is not surprising that Avp has been examined in these individuals. Unfortunately, the data appear to be contradictory. A study by Coccaro and colleagues[165] found a positive correlation between Avp in the CSF of personality-disordered individuals that have a life history of aggressive behavior. Whereas another study found no differences in CSF Avp between violent offenders and controls.[166] It may be that differences in the populations studied account for the inconsistency in the findings, but it seems that more work in this area is warranted.

Schizophrenia

There are three broad categories of symptoms that characterize schizophrenia: (1) positive (e.g., hallucinations and delusion), (2) negative (e.g., anhedonia, impaired social behavior), (3) cognitive/attentional (e.g., impaired memory and executive function). Thus far, most of the work implicating a role for Oxt in aspects of schizophrenia comes from animal models.[167-169] However, in humans, while its role has remained controversial, Oxt has been linked to schizophrenia since the 1970's when it was used as an antipsychotic.[170,171] The data are mixed with regards to Oxt and schizophrenic populations, with one study reporting increases in plasma Oxt concentrations,[172] another study reporting no change,[173] and a third reporting decreases.[174] Though, similar to measures of Avp in individuals with personality disorder, these discrepancies may reflect differences in the populations of those that were studied.

Support for a potential role for Avp comes from studies indicating that treatment with neuroleptics improves psychiatric symptoms and reduces (or normalizes) Avp in blood plasma.[175,176] In studies using an animal model that lacks Avp, the Brattleboro rat, there are reports of deficits in behaviors associated with schizophrenia, specifically, social discrimination and prepulse inhibition of the startle reflex; these deficits can be rescued following treatment with antipsychotics.[177-181] It may be that Oxt and Avp only contribute to certain aspects of schizophrenia, such as the cognitive and social behavior deficits, within specific populations. Since treatment with antipsychotics often does not significantly improve the cognitive and negative symptoms associated with schizophrenia, it is important continue to investigate the neurobiology that underlies these behaviors.

CONCLUSION AND FUTURE DIRECTIONS

This is an exciting time for the neurobiology of sociability. The roles of Oxt and Avp are being explored and a more complete understanding of how these neurohormones interact with other neurotransmitter and neurohormone systems, such as dopamine and corticotropin releasing factor, are beginning to emerge.[71,182-188] There is diversity in the animal models being used, ranging from comparative studies to transgenic studies, that have revealed remarkable conservation in the roles of Oxt and Avp across species. Research examining sociability in humans is on the rise and with the use of pharmacological, genetic and imaging tools the link between the animal models of sociability and human behavior is becoming less tenuous. Further, in human neuropsychiatric disorders characterized by impaired sociability, the roles of Oxt and Avp are being elucidated and better pharmacological agents are being developed.[189-192]

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