Published in final edited form as:
Prog Neurobiol. 2008 January ; 84(1): 1–24.

Vasopressin: Behavioral Roles of an "Original" Neuropeptide

Heather K. Caldwell[†,§], **Heon-Jin Lee**[†], **Abbe H. Macbeth**[†], and **W. Scott Young III**[*]
Section on Neural Gene Expression, NIMH, NIH, DHHS, Bethesda, MD 20892

Abstract

Vasopressin (Avp) is mainly synthesized in the magnocellular cells of the hypothalamic supraoptic (SON) and paraventricular nuclei (PVN) whose axons project to the posterior pituitary. Avp is then released into the blood stream upon appropriate stimulation (e.g., hemorrhage or dehydration) to act at the kidneys and blood vessels. The brain also contains several populations of smaller, parvocellular neurons whose projections remain within the brain. These populations are located within the PVN, bed nucleus of the stria terminalis (BNST), medial amygdala (MeA) and suprachiasmatic nucleus (SCN).

Since the 1950's, research examining the roles of Avp in the brain and periphery has intensified. The development of specific agonists and antagonists for Avp receptors has allowed for a better elucidation of its contributions to physiology and behavior. Anatomical, pharmacological and transgenic, including "knockout," animal studies, have implicated Avp in the regulation of various social behaviors across species.

Avp plays a prominent role in the regulation of aggression, generally of facilitating or promoting it. Affiliation and certain aspects of pair-bonding are also influenced by Avp. Memory, one of the first brain functions of Avp that was investigated, has been implicated especially strongly in social recognition. The roles of Avp in stress, anxiety, and depressive states are areas of active exploration. In this review, we concentrate on the scientific progress that has been made on understanding the role of Avp in regulating of these and other behaviors across species, as well as discuss the implications for human behavior.

1. Introduction

The neurohypophysial hormone arginine vasopressin (Avp) was originally detected by Oliver and Schäfer (1895) who demonstrated that extracts of the pituitary altered blood pressure. Subsequently, the antidiuretic properties of Avp were discovered (Farini, 1913; Vongraven, 1913). However, it was not until du Vigneaud and colleagues (1952) isolated the peptide that specific activities could be ascribed. Following this finding, the nine amino acid sequence and structures of Avp (Turner et al., 1951; Archer and du Vigneaud, 1953; du Vigneaud et al., 1953a) and the related hormone oxytocin (Oxt) (Tuppy, 1953; du Vigneaud et al., 1953b) were elucidated, followed shortly by their synthesis (du Vigneaud et al., 1954a; du Vigneaud et al., 1954b). In 1955, du Vigneaud won the Nobel Prize in Chemistry due, in part, to his early descriptions and syntheses of Avp and Oxt.

[*]Corresponding Author: 9000 Rockville Pike, Building 49, Room 5A60, Bethesda, MD 20892-4483. Email: wsy@mail.nih.gov
[†]These authors contributed equally
[§]Current address: Kent State University, Department of Biological Sciences, PO Box 5190, Kent, OH, 44242.

Avp is mainly synthesized in the magnocellular cells of the hypothalamic supraoptic (SON) and paraventricular nuclei (PVN) whose axons project to the posterior pituitary (Brownstein et al., 1980; Young and Gainer, 2003). Avp is then released into the blood stream upon appropriate stimulation (e.g., hemorrhage or dehydration) to act at the kidneys and blood vessels (Nishimura and Fan, 2003). The brain also contains several populations of smaller, parvocellular neurons whose projections remain within the brain. These populations are located within the PVN, bed nucleus of the stria terminalis (BNST), medial amygdala (MeA) and suprachiasmatic nucleus (SCN) (Buijs et al., 1978; De Vries and Buijs, 1983; De Vries et al., 1985). Other studies suggest that Avp may be more widely expressed in the brain but at significantly lower levels (Planas et al., 1995; Hallbeck et al., 1999).

Since the 1950's, research examining the roles of Avp in the brain and periphery has intensified. The development of specific agonists and antagonists for Avp receptors has allowed for a better elucidation of its contributions to physiology and behavior (Manning and Sawyer, 1991; Barberis et al., 1999; Serradeil-Le Gal et al., 2002a). Anatomical, pharmacological and transgenic, including “knockout,” animal studies, have implicated Avp in the regulation of various social behaviors across species. Enough scientific progress has been made that we are now gaining a better understanding of Avp from its transcription to its regulation of behavior.

1.1 Structure and evolution of vasopressin

The Avp gene contains three exons and two introns (see Fig. 1). It is on the same chromosome as Oxt (chromosome 2 in mice and chromosome 20 in human), but oriented in the opposite transcriptional direction (Mohr et al., 1988;Hara et al., 1990), implying that these two genes were duplicated during evolutionary development. Avp peptide has a ring structure formed by a disulfide bridge and differs from Oxt at two amino acid residues (Hruby et al., 1990). The two genes are separated by an intergenic region (IGR) which is about 11 kbp in rat and human, and 3.6 kbp in the mouse (Gainer et al., 2001;Young and Gainer, 2003). Regulatory DNA sequences exist within conserved portions of the IGR (Gainer et al., 2001;Young and Gainer, 2003). The preprohormone consists of the signal peptide, the nonapeptide Avp, and the first nine amino acid residues of the neurophysin protein (encoded by first exon); the central part of the neurophysin (encoded by the second exon); and the C-terminal part of the neurophysin as well as a glycopeptide (encoded by the last exon) (Burbach et al., 2001;Young and Gainer, 2003). Avp is evolutionarily well-conserved as even the primitive organism hydra expresses an Avp-like peptide (Grimmelikhuijzen and Spencer, 1984). The evolutionary progenitor of the vertebrate Avp, vasotocin, is found in birds and reptiles (Acher, 1990).

1.2. Pharmacology of the vasopressin receptors

There are three major receptor types for Avp: Avpr1a, Avpr1b, and Avpr2. The Avp receptors have seven transmembrane domains: Avpr1a and Avpr1b couple to $G_{\alpha q/11}$ GTP binding proteins, which along with $G_{\beta\lambda}$, activate phospholipase C activity whereas Avpr2 couples to Gs and acts through the cyclic AMP system (Michell et al., 1979; Jard et al., 1987). Although not confined to these tissues in the periphery, the Avpr1a is prominent in the liver, kidney and vasculature. The Avpr1b is prominent in the anterior pituitary in cells that make adrenocorticotropin hormone (Antoni, 1984) but is detected in many other tissues (Lolait et al., 1995). Avpr2 is mainly expressed in the kidney and the antidiuretic function of Avp is mostly transduced via this receptor in the renal collecting duct (Bankir, 2001). The Avpr1a and Avpr1b are expressed throughout the brain (see below), but evidence for the presence of the Avpr2 there is scant (Foletta et al., 2002). A review of the receptor structures and ligand interactions is available (Thibonnier et al., 2002).

The search for specific agonists and antagonists for the Avp receptors has been an active area of research (Chan et al., 2000; see Table 1). In general, agonists for the receptors have been

modifications of vasopressin whereas smaller organic compounds have been developed as antagonists (Serradeil-Le Gal et al., 2002), though few practical uses have been found. Desmopressin (1-desamino-8-d-arginine vasopressin, DDAVP), which acts at the Avpr2 in the renal collecting ducts, is used in patients with central diabetes insipidus to reduce urine production (and water loss) (Robinson, 1976). Vasopressin itself is used to increase blood pressure in patients with shock (Wenzel et al., 2004; Grmec and Mally, 2006). Avpr2 antagonists alleviate the effects of hypernatremia in patients with the syndrome of inappropriate secretion of antidiuretic hormone (Saito et al., 1997; Serradeil-Le Gal et al., 2002; Wong et al., 2003).

The recent development of orally active antagonists shows potential in treating some mental disorders based on animal studies. In particular, the Avpr1b antagonist, SSR149415, produces reduced aggression and anxiety-like behaviors in rodents (Griebel et al., 2002; Blanchard et al., 2005; Stemmelin et al., 2005). The Avpr1a antagonist also reduces aggression in hamsters (Ferris et al., 2006). A full description of these effects can be found in sections 2.2.1 and 2.4.

1.3. Distribution (expression) of the vasopressin receptors in the brain

The distribution of Avpr1a expression within the central nervous system (CNS) has been primarily studied using receptor autoradiography and hybridization histochemistry. Receptor autoradiography identifies the locations of binding to the receptor protein, whereas hybridization histochemistry identifies the cells that transcribe the receptor gene. Prominent Avpr1a binding (Fig. 2) is present in the rat lateral septum (LS), neocortical layer IV, hippocampal formation, amygdalostriatal area, BNST, various hypothalamic areas (including SCN), ventral tegmental area, substantia nigra, superior colliculus, dorsal raphe, nucleus of the solitary tract and inferior olive (Johnson et al., 1993). Avpr1a binding is moderate throughout the spinal cord, but binding is higher in the dorsolateral motoneurons in general and all motoneurons in the lumbar 5/6 levels, where innervation to the perineal muscles originates (Tribollet et al., 1997).

Neurons containing Avpr1a transcripts are found extensively throughout the rat CNS, with prominent expression in the olfactory bulb, hippocampal formation, LS, SCN, PVN, anterior hypothalamic area, arcuate nucleus, lateral habenula, ventral tegmental area, substantia nigra (pars compacta), superior colliculus, raphe nuclei, locus coeruleus, inferior olive, area postrema and nucleus of the solitary tract (Ostrowski et al., 1994; Szot et al., 1994). Transcripts are also detected in the choroid plexus and endothelial cells. The distributions of Avp binding have been examined in a number of rodent species and they are remarkably similar. Differences in binding in selected areas may mediate important adaptations or behavioral traits (see section 2 on Behavior).

The Avpr1b was initially described in the anterior pituitary (Antoni, 1984). Avpr1b transcripts as well as Avpr1b immunoreactive cell bodies have been found in the rat brain, including the olfactory bulb, piriform cortical layer II, septum, cerebral cortex, hippocampus, PVN, SCN, cerebellum, and red nucleus (Lolait et al., 1995; Saito et al., 1995; Vaccari et al., 1998; Hernando et al., 2001; Stemmelin et al., 2005). It should be noted, however, that Avpr1b distribution has not been mapped by receptor autoradiography due to the lack of a specific radiolabeled ligand. A recent study using in situ hybridization histochemistry with specific probes found particularly prominent Avpr1b expression in the hippocampal field CA2 pyramidal neurons (Young et al., 2006).

1.4. Sex differences in the expression of vasopressin and its receptors

Behaviors often differ between the sexes, so there has been great interest in mapping sex-related differences in the Avp system. The pioneering studies of De Vries and colleagues (1983) have

shown that the density of Avp fibers in the LS is elevated in males compared to females and that testosterone administered to females and castrated males increases the density of Avp fibers within the LS. Similarly, gonadectomy in males or females reduces Avp in certain regions of the brain that receive innervation from the BNST and MeA, but no reduction in regions that receive innervation from the magnocellular neurons of the PVN and SON (De Vries et al., 1984; De Vries et al., 1985). Avp mRNA levels in the BNST and MeA are also testosterone dependent (Miller et al., 1989; Miller et al., 1992; Wang and De Vries, 1995). Curiously, gonadectomy has no effect on Avp immunoreactivity in Syrian hamsters (Albers et al., 1991), but it does affect Avp immunoreactivity in Siberian hamsters (Dubois-Dauphin et al., 1994). Therefore, it is not clear how widely this gonadal steroid-dependency is conserved across mammals. Also, in chronically hyperosmolar rats there is evidence that gonadal steroids may modulate Avp expression (Crowley and Amico, 1993; O'Keefe et al., 1995). There is also evidence for an interaction between gonadal steroids and Avp, as androgen receptors are found in non-magnocellular responsive neurons (Zhou et al., 1994), and estrogen receptor beta is expressed in Avp magnocellular neurons (Alves et al., 1998). An estrogen responsive element is found over 4 kbp upstream of the transcriptional start site of the rat Avp gene (Shapiro et al., 2000), but whether this is where androgens and/or its metabolites exert their effects is unknown.

Avpr1a transcription and translation are sensitive to gonadal steroids in the brain but more research is warranted. In the photoperiodic Syrian and Siberian hamsters, exposure to short “winter-like” photoperiods results in dramatic reductions in Avpr1a binding within brain areas associated with the neural regulation of social behavior (Dubois-Dauphin et al., 1994; Caldwell and Albers, 2003; Caldwell and Albers, 2004a). Likewise, gonadectomy and lactation can decrease Avpr1a mRNA and receptor binding within the hypothalamus (Delville et al., 1995; Johnson et al., 1995; Young et al., 2000). In young rats, estrogen increases Avpr1a mRNA in the preoptic area of the hypothalamus (Funabashi et al., 2000). Castration has been reported to reduce binding in the pudendal nuclei of lumbar 5/6 levels (Tribollet et al., 1997). There is no evidence yet for any sex differences in the expression of the Avpr1b.

1.5. Gene inactivation in mice

The mouse shares many, if not most, aspects of anatomy, biochemistry and physiology with humans. This is not too surprising given that about 99% of mouse protein-coding genes have human counterparts (and vice versa) and justifies the research effort expended on generating and studying transgenic mice, including those produced through homologous recombination (“knockout”, KO, −/−) (Tecott, 2003).

A knockout of the Avp gene has not been published to our knowledge, although a natural occurring Avp mutant, the Brattleboro rat, has been extensively studied (Bohus and de Wied, 1998; Grant, 2000). The key observation in this line is diabetes insipidus that results in increased thirst-driven behavior. Studies of behavioral deficits in this line are discussed below (see Section 2).

The first of the Avp receptors to be inactivated was the Avpr2 (Yun et al., 2000). The Avpr2 gene is located on the X chromosome, so the male hemizygous and female Avpr2 KO pups cannot concentrate their urine. These pups also show enlarged renal pelvic spaces and die within the first week after birth due to hypernatremic dehydration. Female heterozygous mice display normal growth but have a moderate diabetes insipidus phenotype with polyuria, polydipsia and reduced ability to concentrate urine (Yun et al., 2000).

The initial report for Avpr1a KO mice indicated a function for the Avpr1a as a negative regulator of B cell receptor signaling, suggesting a role for Avp in stress-related immune responses (Hu et al., 2003). A different KO line of the Avpr1a demonstrates a lower basal blood

pressure (Egashira et al., 2004; Koshimizu et al., 2006) and impaired lipid metabolism and glucose homeostasis (Aoyagi et al., 2007; Hiroyama et al., 2007). Both lines have changes in behavior as discussed below.

The initial descriptions of the Avpr1b KO reported reduced aggressive behavior and social motivation (Wersinger et al., 2002; Wersinger et al., 2004) as further discussed below. Tanoue and colleagues also generated Avpr1b −/− mice and showed attenuated catecholamine and hypothalamic-pituitary-adrenal (HPA) axis responses to stress (Tanoue et al., 2004) as well as reduced Avp responses in the pancreas for both insulin and glucagon (Oshikawa et al., 2004; Fujiwara et al., 2007). The HPA responses to the acute insulin-induced hypoglycemic and chronic restraint stresses are also impaired (Lolait et al., 2007).

2. Behavior

The roles of Avp in the neural regulation of various behaviors, especially social behaviors, are irrevocably intertwined. Therefore, for the purposes of this review we have separated behavior into three broad categories: social behaviors; learning and memory (social and non-social); stress; and anxiety and depression. While there will be some overlapping themes, a concerted effort has been made to draw out the similarity in the roles of Avp across these behaviors. Also, it should be noted that while Avp is often discussed in concert with Oxt, the primary focus of this paper is Avp, though it should be recognized that the Oxt literature is very complementary and there are some excellent recent reviews exploring the behavioral roles of both neuropeptides (Keverne and Curley, 2004; Caldwell and Young, 2006; Hammock and Young, 2006; Lim and Young, 2006).

2.1 Regulation of behavior by the suprachiasmatic nucleus

All mammals' behaviors are influenced by a central circadian clock, located within the SCN. The SCN, entrained through input via the retinohypothalamic pathway, controls circadian activity through feedback loops of a number of ‘clock genes’ (for review, see Albrecht and Eichele, 2003; Kalsbeek et al., 2006b).

Avp was the first neurotransmitter described in the SCN, and is one of the major neuropeptides produced there. It is the only neurotransmitter to date that has been shown to be released in a circadian rhythm in vivo. Avp displays circadian rhythmicity of release into the cerebrospinal fluid (CSF), with peak release during the day in a light-dark cycle (Reppert et al., 1983). Avp in the SCN aids in circadian control of hormone secretion. Avp-immunoreactive (Avp-ir) neurons have terminals in the PVN, which synthesizes and releases corticotrophin releasing hormone (Crh) and subsequent adrenocorticotropic hormone (ACTH) secretion from the pituitary. Avp from the SCN seems to exert a controlling effect of secretion of Crh and ACTH, with a primarily inhibitory role (for review, see Buijs et al., 2003; Perreau-Lenz et al., 2004; Kalsbeek et al., 2006a; Kalsbeek et al., 2006b). There is also a polysynaptic pathway from the SCN to the adrenal glands via the intermedio-lateral column of the spinal cord and sympathetic outflow (Buijs et al., 1999). Furthermore, Avp may aid in control of the hypothalamic-pituitary-gonad axis in females (see Buijs et al., 2003; Perreau-Lenz et al., 2004 for review).

Wheel-running activity in rodents is an indicator of circadian rhythmicity, with increased activity during the dark phase of the light-dark cycle in nocturnal species. While it is only correlational, diurnal fluctuations in Avp may exert some control over this behavior. In common voles, *Microtus arvalis*, fewer Avp-positive neurons are found in the dorsomedial SCN of highly rhythmic animals as compared to non-rhythmic animals kept in a light-dark cycle (Gerkema et al., 1994). Similar results were found *in vitro*, as SCN cultures prepared from voles with rhythmic wheel-running activity patterns contain significantly fewer Avp-ir cells than cultures from non-rhythmic voles (Jansen et al., 1999). Voles lacking rhythmic

activity patterns do not produce a circadian pattern of Avp release (Jansen et al., 2000), indicating that Avp release is hampered in non-rhythmic voles (the Avp release deficit hypothesis), which may account for higher Avp-ir cells in non-rhythmic voles (Gerkema et al., 1994; Jansen et al., 2000). Furthermore, in the vole Avp contributes to circadian rhythmicity throughout the lifespan. Aging leads to decreased circadian activity patterns: 75% of old voles (11.5 months old), as compared to only 33% of young voles (4.5 months old) are non-rhythmic (Van der Zee et al., 1999). Avp is likely involved, as the number of Avp-ir SCN cells decreases over 78% from young to old voles (Van der Zee et al., 1999).

Avp influences on circadian rhythmicity are not limited to voles, but can be found in other rodent species. European ground squirrels, *Spermophilus citellus*, have absent or suppressed circadian rhythmicity when first emerging from hibernation; spontaneous regeneration of rhythmicity correlates positively with the number of Avp-ir neurons in the SCN (Hut et al., 2002). In two mice lines selected for nest-building behavior, differences in circadian rhythms are accompanied by different number of Avp-ir neurons in the SCN, as well as different transport and release of Avp in the SCN (Van der Veen et al., 2005). Reduced diurnal rhythms of Avpr1a mRNA in the SCN are seen in aged (19-20 months old), compared to young, rats (2-3 months old) (Kalamatianos et al., 2004). Evidence in golden hamsters, *Mesocricetus auratus*, indicates that lesions to the SCN reduce the number of Avp-ir fibers throughout the brain, but seem to affect only circadian locomotor behavior (wheel running), and not another Avp-dependent behavior, flank marking (see section 2.2.1) (Delville et al., 1998). Thus, evidence from a variety of rodent species implicates Avp in the SCN to be important for circadian rhythmicity of locomotor behavior.

However, despite the evidence above, the complete absence of Avp in Brattleboro rats (Groblewski et al., 1981) fails to alter circadian rhythms. Even in Avpr1a −/− mice there is only a modest effect on the circadian system. Specifically, a lengthened tau has been observed, which, while affecting the period, has no impact on rhythmicity per se (Wersinger et al., 2007b). Furthermore, the diurnal rhythm of mutant Avp mRNA and of the Avpr1a mRNA in the SCN persists in the absence of Avp in rats (Young et al., 1993). It is unclear whether these latter results signify developmental compensation, the relative unimportance of Avp in regulating circadian rhythms, or that arrhythmic animals may have altered Avp due to a malfunctioning SCN, and not the other way around.

The influence of SCN-derived Avp in human and non-human primate circadian rhythms has primarily been examined in relation to aging, dementia, and depression. Changes in circadian rhythms, particularly sleep irregularities, have been found in both healthy and ailing elderly persons (for review, see Myers and Badia, 1995; Van Someren, 2000). In people under 50 years old, Avp content within the SCN shows a clear circadian pattern; this pattern is reversed in those over 50 (Hofman and Swaab, 1994). The diurnal rhythm of Avp is reported to be absent in patients with hydrocephalus (Barreca et al., 1988). Patients with Alzheimer's disease have over 30% less Avp mRNA in the SCN than do healthy age-matched persons (Liu et al., 2000; Ishunina and Swaab, 2002). Decreased Avp mRNA is seen in Alzheimer's patients both with and without depression, although other work has found greater Avp-ir neurons in the SCN of elderly patients with depression as compared to age-matched controls (Zhou et al., 2001). It is possible that synthesis and release of Avp is reduced in depressed patients and those with Alzheimer's disease, which could contribute to the disturbances in circadian rhythmicity that are prevalent in both disorders.

2.1 Social Behavior

Working in concert, affiliation and aggression are used to maintain appropriate interactions within a social group. Aggression permits better access to resources whereas affiliative interactions allow for reproductive behavior, parental behavior, and even monogamy in some

mammalian species. Across species, Avp is important in the regulation of both aggression and affiliation though, in general, predominantly in males. The next sections will delve into the role of Avp in the regulation of aggression and affiliation. Table 2 summarizes the effects of Avp on the social and non-social behaviors discussed below.

2.2.1. Aggression—Aggression is critical to an animal's survival, allowing for better access to food and mates and, in general, conveying evolutionary fitness. Often classified into 5 categories: offensive aggression, defensive aggression, maternal aggression, play fighting, and predatory aggression, aggression is an integral part of most mammalian societies (Miczek et al., 2001; Blanchard et al., 2003). Studies of the role of Avp in the regulation of aggression have focused on offensive aggression, which in rodents is examined using a resident-intruder test. From this work two important concepts have emerged: 1) Avp primarily modulates intermale aggression and 2) Avp-facilitated aggression appears to be dependent upon prior experience, suggestive of synaptic learning and/or epigenetic regulation of gene expression. Also, while key anatomical sites have been identified, their interactions with one other, as well as the interactions of Avp with other neurotransmitter systems are still poorly understood. The vasopressinergic projections from the BNST and MeA to the caudal LS are important for aggression and are androgen-dependent (De Vries et al., 1984; De Vries et al., 1985; van Leeuwen et al., 1985; Caffe et al., 1987; Compaan et al., 1993; De Vries and Miller, 1998). The anterior hypothalamus (AH) is also consistently implicated in the regulation of aggression and Avpr1a in this area demonstrates considerable plasticity, which is discussed in section 2.1.1.2 (Ferris et al., 1989; Albers et al., 2006; Askew et al., 2006). Lastly, there is emerging evidence that the Avpr1b is critical for aggression though the neural substrate(s) involved have yet to be identified (Wersinger et al., 2002; Wersinger et al., 2007a) (see Fig. 3).

2.2.1.1. Pharmacological and behavioral manipulations: The most comprehensive work describing the role of Avp in the regulation of aggression has been carried out in Syrian hamsters. As they are a solitary species, Syrian hamsters are highly aggressive towards conspecifics. They also exhibit a stereotypic form of scent marking behavior, known as flank marking, that is displayed more prominently by socially dominant animals (Siegel, 1985). The initial, seminal finding that Avp microinjected into the medial preoptic-anterior hypothalamic area (MPOA-AH) results in a dose dependent increase in flank marking behavior (Ferris et al., 1984) set the framework for future studies in this species and was one of the first to induce a complex behavior by microinjection of a single neuropeptide. These effects of Avp on flank marking are attributed specifically to Avp's action via the Avpr1a since Avpr1a antagonists administered orally or injected into the MPOA-AH block Avp-facilitated flank marking behavior (Ferris et al., 1988; Ferris et al., 1993; Caldwell and Albers, 2003; Ferris et al., 2006). Similarly, aggression can be facilitated when Avp is microinjected into the AH (Ferris et al., 1997; Caldwell and Albers, 2004b) and inhibited when Avpr1a antagonists are microinjected there (Ferris and Potegal, 1988). Superimposed on this system is the influence of gonadal steroids. While Avp innervation of the MPOA-AH is not gonadal steroid dependent (Albers et al., 1991), Avpr1a biosynthesis is (Johnson et al., 1995; Young et al., 2000).

Other brain areas are also involved in the regulation of aggression. For example, Avpr1a binding within the ventrolateral hypothalamus is gonadal steroid-dependent, and this decrease is correlated with reduced aggression, specifically the initiation of aggression (Delville et al., 1996b). Recent work has implicated the Avpr1b in the regulation of aggression in Syrian hamsters. Hamsters administered an oral Avpr1b antagonist display less aggression than untreated controls (Blanchard et al., 2005), though some of the more compelling evidence for the role of the Avpr1b in the regulation of behavior is described below in section 2.2.1.3 (Transgenics).

One of the lingering questions in this field is the interplay between flank marking and aggression. While they are complementary behaviors that help an animal attain and maintain dominance, and appear to be regulated by some of the same neuroanatomical areas, they are not necessarily behaviors that are a part of a behavioral continuum. For instance, the specific site where Avp stimulates aggression is different than the one that stimulates flank marking. Also, the doses of Avp used to induce aggression and flank marking differ (Albers et al., 1988; Ferris et al., 1997; Caldwell and Albers, 2003; Caldwell and Albers, 2004b). This does not, however, preclude the possibility that endogenous Avp release in the same brain areas is responsible for the initiation of both behaviors. However, it is likely that the neural regulation of aggression is more complex and the circuits more redundant than that of flank marking.

Comparable data have been found in other species, but some of the neuroanatomical areas differ from those described in hamsters. In prairie voles there is evidence that Avp may be important to increases in aggression seen following pair-bond formation. Specifically, compared to controls, pair-bonded males that show high levels of aggression towards unfamiliar conspecifics have increased c-fos activation within the AH; specifically, within cells that contain Avp and tyrosine hydroxylase. The authors suggest that Avp within the AH may be important for processing chemosensory cues or responding to them (Gobrogge et al., 2007).

There is some elegant work examining differences between mice that have been bred for either a long attack latency or short attack latency. Studies of these mice have provided valuable insights into critical differences between highly aggressive individuals and their less aggressive counterparts. For instance, short attack latency mice have less Avp-ir innervation in the LS and fewer Avp-ir neurons in the BNST than long attack latency mice (Compaan et al., 1993). The findings are similar in rats in which there is a negative correlation between Avp and aggression in the LS (Everts et al., 1997). The opposite is found in *Peromyscus californicus* (California mouse) which are more aggressive than *Peromyscus leucopus* (white-footed mouse) and have a positive correlation between aggression and Avp-ir in the BNST and LS (Bester-Meredith and Marler, 2001). In prairie voles and California mice, intracerebroventricular (i.c.v.) injections of Avpr1a antagonists inhibit aggression and in prairie voles injections of Avp increase aggression (Winslow et al., 1993; Bester-Meredith et al., 2005). However, the authors suggest that Avp antagonists do not block the expression of aggression *per se*, as breeder males with established aggression are unaffected; but, rather, affect the transition to aggression, i.e. initiation of aggression. The idea that the effects of Avp on aggression are dependent on an animal's history is supported by several studies and discussed in more detail below.

2.2.1.2. Experience-dependent changes: The ability to display territorial aggression is susceptible to manipulation depending on an individual animal's early life experience and/or social status. This plasticity in aggression is linked with changes in either Avp or Avp receptor distributions in a variety of mammalian species (e.g. Roche and Leshner, 1979; Ferris et al., 1988; Melloni et al., 1997; Stribley and Carter, 1999; Frazier et al., 2006). The next sections will detail the experience-dependent changes in Avp and its receptors, and how they relate to aggression.

2.2.1.2.1. Early life experience: While sexually naïve prairie voles generally do not show territorial aggression, early postnatal exposure to Avp can increase displays of aggression similar to levels seen in post-mated animals (Stribley and Carter, 1999). Newborn California mice that are retrieved more by their fathers show higher levels of aggression in adulthood than mice that are retrieved less. These animals also have increased Avp-ir fibers in the dorsal fiber tracts of the BNST (Frazier et al., 2006). Adult male rats that undergo maternal separation as pups have higher aggression, more Avp mRNA and Avp immunoreactivity in the PVN and SON, perhaps due to poor stress-coping as these animals also show more depression-like

activity during, and an increased ACTH response following, forced swim tests (Veenema et al., 2006).

Some interesting work in hamsters has focused on the impact of exposure to anabolicandrogenic steroids during the androgen sensitive time of adolescence on adult aggressive behavior. Not only does exposure to anabolic-androgenic steroids during adolescence increase adult aggression, but it also increases Avpr1a-ir within the AH, though the effects appear to be reversible following cessation of treatment (Grimes et al., 2006). In anabolic-androgenic steroid-treated animals that have an Avpr1a antagonist microinjected into the AH, there is a reduction in the intensity, but not the initiation, of aggression (Melloni et al., 1997; Harrison et al., 2000).

2.2.1.2.2. Social status: Initial studies suggested that Avp might have differential effects on aggression in dominant versus subordinate animals. Mice administered lysine-vasopressin just after a social defeat, increase their submissive behavior on subsequent tests compared to saline treated animals (Roche and Leshner, 1979). Further, injections into the MPOA-AH results in transient reversals of dominate/subordinate relationships in Syrian hamsters, with subordinate animals displaying increased flank marking behavior when treated with Avp and dominant animals less flank marking behavior when treated with dPTyr(Me)AVP, an Avpr1 antagonist (Ferris et al., 1986). Consistent with these findings, subordinate hamsters have fewer Avp-ir perikarya in the magnocellular nucleus circularis compared to dominant animals (Ferris et al., 1989). Following repeated agonistic encounters, dominant hamsters have more Avpr1a binding in the ventromedial hypothalamus compared to their subordinate opponents (Cooper et al., 2005). In socially isolated hamsters, there is an increase in aggression that correlates with increased Avpr1a binding in the AH, PVN and lateral hypothalamus, whereas in socially experienced hamsters Avpr1a binding is significantly greater in the central amygdala (Albers et al., 2006). Even in Avp-facilitated aggression, several weeks of social isolation is required for Avp to be effective, suggesting that social experience, or lack there of, is critical for the effects of Avp on aggression (Ferris et al., 1997; Caldwell and Albers, 2004b). In rats, dominant animals (as determined by food competition) have more Avpr1a binding in the LS compared to subordinates. These differences in receptor binding are not testosterone- or corticosterone-dependent, suggestive of experience-dependent changes in the Avp system (Askew et al., 2006). Taken together, there is substantial evidence that the Avp system, and specifically Avpr1a biosynthesis, can be altered by social experience.

2.2.1.3. Transgenics: The generation of mice with inactivation of the either the Avpr1a or Avpr1b genes has provided insights into their roles in the regulation of aggression. While it was expected that Avpr1a KO mice would show reduced aggression due to lack of Avp signaling, this was not the case (Wersinger et al., 2007b). This is likely due to developmental compensation and is not thought to reflect the true role of Avpr1a in the modulation of aggression. Conversely, Avpr1b appears to be critical for proper expression of aggression, as Avpr1b −/− mice show significant impairments in displays of aggression as compared to wildtype controls (Wersinger et al., 2002; Wersinger et al., 2004; Wersinger et al., 2007a). In addition, an orally administered Avpr1b antagonist reduces aggression in mice and hamsters (Blanchard et al., 2005; for review see Serradeil-Le Gal et al., 2005). Avpr1b −/− mice have longer attack latencies and fewer attacks compared to wildtype controls, though the latencies and frequencies of attack can be increased with experience (Wersinger et al., 2002; Wersinger et al., 2007a). These impairments are specific to social forms of aggression, as predatory aggression remains unaffected. Furthermore, only the attack component is affected, as the Avpr1b KO display defensive postures but do not initiate defensive or “retaliatory” attacks (Wersinger et al., 2007a). The actions of Avp via Avpr1b are not sexually dimorphic since female Avpr1b −/− mice show reduced maternal aggression (Wersinger et al., 2007a). Avpr1b may not be involved in the transduction of the olfactory signals, but rather in coupling the

social context with the appropriate behavioral response (Wersinger et al., 2004). Given the restricted distribution of Avpr1b mRNA within the brain, with highest expression within the CA2 field of the hippocampus, it may be that the Avpr1b is important for "social memory" for which an aggressive response would be appropriately triggered (Young et al., 2006). Future studies that focus on the specific neuroanatomical areas involved in Avpr1b's mediation of aggression will be important for understanding the role of Avp in the regulation of aggression.

2.2.1.4. Vasopressin and serotonin: Whereas Avp facilitates aggression and serotonin (5-HT) inhibits aggression, their exact relationship remains elusive. Within the ventrolateral hypothalamus, 5-HT blocks Avp-facilitated offensive aggression (Delville et al., 1996a). In the AH, a Htr1a, but not a Htr1b, serotonin receptor agonist produces a dose-dependent inhibition of Avp facilitated offensive aggression (Ferris et al., 1999). The 5-HT innervation to this area is traced to the dorsal, median, and caudal linear raphe nuclei (Ferris et al., 1999). Likewise, treatment with selective serotonin re-uptake inhibitors suppresses Avp-facilitated flank marking behavior (Ferris et al., 2001). In rats that have undergone maternal separation, and who subsequently show higher levels of aggression, 5-HT-ir in the AH and SON negatively correlates with aggression (Veenema et al., 2006). With their opposing effects on aggression, Avp and 5-HT are biologically interconnected, and studies focusing on their interactions are critical to increasing our understanding of the neural regulation of aggression.

2.2.1.5. Humans: In humans, heightened aggression is associated with increased impulsivity and is a characteristic of individuals with personality disorders. There is a positive correlation of CSF Avp concentration with a life history of non-directed general aggression (including temper tantrums and property assault) as well as aggression towards individuals (Coccaro et al., 1998). Similar to rodent models, this finding is suggestive of an enhancing effect of Avp on aggression, although it should be noted that not all studies are in agreement. A study by Virkkunen and colleagues (1994) found no differences in CSF Avp between violent offenders and controls. These discrepancies, however, may be due to differences in the patient populations being studied.

Intranasal Avp administration, at least in men, is reported to increase the emotional response to neutral stimuli resulting in an increased perception of threat (Thompson et al., 2004; Thompson et al., 2006). Although Born et al. (2002) have shown that intranasal application of Avp increases concentration of Avp in the CSF within 30 minutes of application, and remains elevated for at least 80 minutes, there is no evidence to distinguish between direct entry of Avp versus CNS release of Avp by actions in the periphery. There is also preliminary work examining the differences in levels of autoantibodies for Avp between people with conduct disorder, prisoners, and healthy controls. Individuals with conduct disorder have reduced levels of Avp-reactive antibodies (Fetissov et al., 2006). These authors hypothesize that the autoantibodies could either regulate peptides crossing the blood-brain barrier or centrally interfere with peptides, allowing for elevated Avp and a resulting increase in aggression. Alternatively, greater Avp could influence the HPA axis (through the anterior pituitary's Avpr1b), as is hypothesized for ACTH and autoantibodies (though the adrenal glands) (Fetissov et al., 2006). The effects of peptide autoantibodies on behavior are just now beginning to be explored but provide an interesting and a previously unexplored mechanism by which to regulate behavior.

2.2.1.6. Conclusion: Given the difficulty of studying and the complexity of aggression in humans, the concordance between the findings of the animal work and that of the human literature implicating Avp in the regulation of aggression is compelling. It appears that the role of Avp in the regulation of aggression is highly conserved. It will be interesting to see what insights are gained through the use of more focused and refined genetic tools to identify specific

interactions between neuroanatomical areas and different neurotransmitter systems in the regulation of aggression.

2.2.2. Affiliation—Affiliation encompasses social bonding between individuals, including sexual partner relationships and parent-infant relationships. The formation of social bonds helps increase security thereby reducing stress and anxiety. The ways in which social bonds are formed are species-specific and show high individual variability (for review see Carter, 1998). In the sections below we will explore the contributions of Avp to the regulation of pair bonding and parental behavior.

2.2.2.1. Pair bonding: Found in fewer than 5% of mammalian species, monogamy is defined as an exclusive, long-lasting sexual relationship between partners (Kleiman, 1977). Monogamy can also be defined using a group of distinguishing characteristic behaviors described by Carter and colleagues (1995) that include: 1) cohabitation and long-term pair bonding in the breeding and non-breeding season, 2) aggressive displays towards unfamiliar conspecifics, 3) biparental care, 4) socially regulated reproduction and 5) incest avoidance. The formation of pair bonds has been studied almost exclusively in voles, as the genus *Microtus* contains both monogamous (prairie and pine voles) and non-monogamous (montane and meadow voles) species. These voles have been vital in furthering our understanding of social bonding since the biology and behavior of these animals is so diverse, yet can be readily compared.

In the laboratory, pair bonding is measured using a partner preference test. In this test a male and female vole are mated for 24 hours and then separated. The male is then placed into the center of a three chamber apparatus and the amount of time he spends in adjacent chambers, one of which houses the mated (partner) female and the other which houses a novel “stranger” female, is measured (Carter and Getz, 1993; Williams et al., 1994; Carter et al., 1995). A partner preference is said to have occurred when the male spends twice as much time with his partner than the novel “stranger” female.

In voles, distribution of the Avpr1a may underlie differences in social organization as reflected by performance on the partner preference test. Prairie voles have less Avp immunoreactivity and binding in the LS and more in the amygdala compared to montane voles (Insel et al., 1993; Insel et al., 1994). While this is only correlative, more substantive evidence is found in prairie voles administered Avp and Avpr1a antagonists. When administered i.c.v. prior to mating, Avp antagonists inhibit partner preference whereas Avp infusions facilitate partner preference (Winslow et al., 1993; Cho et al., 1999).

Young and colleagues (Young et al., 1999; Lim et al., 2004b) have suggested that the regulatory region 5′ to the promoter of the Avpr1a gene is responsible for the differences in its distribution. Transgenic mice that have 2.2 kbp of the 5′ flanking region, both exons with the 2.5-kbp intron, and 2.4 kbp of 3′ flanking region of a prairie vole Avpr1a mini-gene have patterns of Avpr1a binding similar to that of prairie voles and show increased affiliative behavior, as measured by the amount of time they investigate and groom an ovariectomized female (Young et al., 1999). Interestingly, non-monogamous montane voles do not show increased affiliative behaviors after Avp is centrally injected, suggesting that the species-specific distribution of Avpr1a is important for the development of affiliative behaviors within a given species (Young et al., 1999). Increased affiliative behavior, as measured by huddling, is also increased through additional Avpr1a expression delivered to the ventral forebrain via a viral vector (Lim et al., 2004b). The vole Avpr1a genes were examined and two differences found: 1) the prairie vole genome contains two copies of the Avpr1a gene and 2) the 5′ regulatory region of Avpr1a of both prairie and pine voles contain a microsatellite sequence comprised of simple sequence repeats interspersed with non-repetitive elements (Young et al., 1999). Further studies showed that, *in vitro*, the microsatellite differences produce differences in reporter gene expression

(Hammock and Young, 2004). Also, wild-caught prairie voles show a high level of variability in Avpr1a density in certain brain regions such as the olfactory bulb, cingulate cortex, amygdala, and ventral pallidum (Phelps and Young, 2003). To test the possibility that these individual differences were due to differences in microsatellite length within the same species Hammock and Young (2005) created two prairie vole breeding lines, one that had a long microsatellite sequence and one that had a shorter microsatellite sequence (746 bp vs 727 bp, respectively). There were regional differences in Avpr1a density between these animals and the F1 generation of the line that contained the lengthened microsatellite sequence tended to show a stronger partner preference than the line with the shortened microsatellite sequence. The implications are that within a given species the microsatellite satellite sequence, which is highly susceptible to mutation, may account for variations in Avpr1a density in specific brain regions.

Recently, Fink and colleagues (2006) showed that the presence of the microsatellite in the Avpr1a gene of 21 *Microtus* species was not predictive of monogamy. However, these findings do not preclude the possibility that variations in Avpr1a expression patterns in vole species account for the monogamous or polygamous behaviors seen (Young and Hammock, 2007). Whether these variations are due to the small differences in microsatellite lengths or some other differences in another part of the Avpr1a gene (or other genes) also awaits further study. For a more in depth review on pair bonding and its genetic regulation, see (Insel, 2003; Aragona and Wang, 2004; Young and Wang, 2004; Lim et al., 2004a; Young et al., 2005; Hammock and Young, 2006; Lim and Young, 2006; Nair and Young, 2006).

2.2.2.2. Parental behavior: ***2.2.2.2.1. Paternal care:*** Most research on paternal behavior has focused on monogamous rodent species, particularly the prairie vole and California mouse. Male prairie voles express greater Avp-ir fibers and neurons in the BNST, LS, and Lhb as compared to females (Wang et al., 1998). This pathway is steroid hormone dependent, as castration reduces Avp expression in these brain regions (Wang and De Vries, 1993; Lonstein et al., 2005), as well as displays of paternal behavior (Wang and De Vries, 1993). In a similar study, however, castration did not reduce the number of Avp-ir fibers in the LS or lateral habenula, and yet increased displays of paternal behavior in virgins (Lonstein and De Vries, 1999). Nonetheless, Avp-ir fibers increase naturally in prairie vole males after cohabitation with a female and just prior to parturition, suggesting these fibers are involved in both sexual and paternal behavior (Bamshad et al., 1994). Indeed, Avp directly affects paternal behavior in the vole as intra-septal Avp increases and Avpr1a antagonist decreases paternal behavior in sexually naïve male prairie voles (Wang et al., 1994). Similarly, when combined, Avp and Oxt antagonists significantly reduce alloparental behavior (care of other's offspring) in sexually naïve males, who then attack pups more (Bales et al., 2004).

Non-monogamous male montane and meadow voles do not naturally demonstrate paternal care. Unlike the prairie vole, in which hypothalamic Avp mRNA increases in males and females in the postpartum period, no change in Avp is observed in either male or female montane voles (Wang et al., 2000). As noted above, Avpr1a distribution differs between the monogamous and non-monogamous vole species, suggesting that these receptors may also regulate paternal behavior (Wang et al., 1998). However, elevating Avp induces paternal behavior in meadow voles by inhibiting pup-directed aggression and increasing paternal behavior in previously aggressive meadow voles (Parker and Lee, 2001). Cohabitation may increase paternal responsiveness in meadow voles, as cohabitating males given an Avp receptor antagonist display significantly less paternal behavior than cohabitating male control voles (Parker and Lee, 2001).

Monogamous male California mice spend more time providing paternal care to their offspring than do polygamous white-footed male mice (Bester-Meredith et al., 1999). Similar to prairie

voles, male California mice have higher Avp-ir staining in the BNST, and more Avpr1a in the LS (Bester-Meredith et al., 1999). California mice are also more aggressive towards intruders in the presence of pups than white-footed mice, which may be similar to maternal aggression in regards to pup care (Bester-Meredith et al., 1999; Bester-Meredith and Marler, 2001). Cross-fostering studies show that offspring aggression, paternal behavior, and Avp-ir staining in the BNST and SON is similar to that of their foster, not biological, parents (Bester-Meredith and Marler, 2001; 2003). Similarly, California mice that are retrieved more by their father have decreased attack latency and greater Avp-ir fibers in the BNST (Frazier et al., 2006). Thus, parenting style alters offspring aggression and display of paternal behavior. These effects appear to be modulated by Avp in the BNST and hypothalamus.

In non-rodent mammalian species, paternal care is found in relatively few species, most notably humans and two species of New World primates (for review see Ziegler, 2000). No studies have yet examined the role of Avp in non-human primate paternal care; however, sexually dimorphic differences in numbers and density of Avp-ir fibers in the BNST of marmosets, similar to those seen in rodents, could influence sexual and paternal behavior in non-human primates (Wang et al., 1997).

2.2.2.2.2. Maternal Care: There is some evidence that Avp aids in maternal care of offspring (see Table 2). In rats, Avp levels and/or release increase during late pregnancy, parturition and lactation in various brain regions, including the SON (Caldwell et al., 1987;Mezey and Kiss, 1991), PVN (Caldwell et al., 1987), septum (Landgraf et al., 1991;Landgraf et al., 1992), and hippocampus (Landgraf et al., 1991). Similar changes have been found in the rabbit, where the size and number of Avpir neurons significantly increase in hypothalamic nuclei from late pregnancy through parturition (Caba et al., 1996). Likely, Avp release may help females to regulate water loss and elevated osmolality that result from pup anogenital licking (and subsequent intake of pup urine) during lactation (Mezey and Kiss, 1991;Caba et al., 1996;Wang et al., 2000). Indeed, female montane voles, who engage in less anogenital licking than female prairie voles, do not display elevated Avp mRNA during lactation as do female prairie voles (Wang et al., 2000). In rats, central Avp release predominates over Oxt release during late pregnancy and parturition, but once suckling begins the pattern of release is reversed (Landgraf et al., 1992).

2.2.2.3. Conclusion: Avp is strongly implicated in affiliative behaviors in males of several species, although its role in female affiliative behavior remains less clear. There has been some recent work exploring the contributions of the dopaminergic reward system to pair-bond formation in prairie voles and its possible interactions with the Avp (and OT) systems (Aragona et al., 2003; Aragona et al., 2006). Understanding the interactions of various neurotransmitter and neuropeptide systems during different “behavior states” continues to be an exciting area of research and will likely provide insight into the regulation of context-appropriate behavioral displays.

2.3. Learning and memory

2.3.1. Social memory and social recognition—The ability to recognize individuals is important for normal affiliation and aggression, as without the capacity to distinguish family or friend from foe it is difficult for an animal to display the appropriate behavior. This social memory depends largely on visual and auditory cues in primates and on olfactory, including pheromonal, cues in rodents. In rodents, it is the processing of olfactory cues and the subsequent olfactory memories that are Avp-dependent. The form of social memory examined in rodents is referred to as social recognition.

Social recognition tests are a specific group of learning and memory tests used to examine the social memory of individual conspecifics. Animals are tested for their natural inclination to investigate a novel animal more than a familiar one. Two different types of social recognition tests are generally employed. The first is a "habituation-dishabituation" test in which a subject animal is exposed to the same "stimulus" animal for repeated trials, resulting in a decrease in investigation, i.e. "habituation". The subject is then presented a novel animal that normally results in an increase in investigation, i.e., "dishabituation." (Winslow and Camacho, 1995). The second is a social discrimination test whereby a subject animal is exposed to a "stimulus" animal and then after some predetermined period of time, such as 30 minutes, a second trial is performed in which an animal is re-exposed to either the same familiar animal or a novel animal. Again, animals normally spend more time investigating the novel animal as opposed to the familiar animal in the second trial (Dantzer et al., 1987).

As noted above, there is compelling evidence that Avp is important for social memory formation and, thus, social recognition. In particular, the androgen-dependent vasopressinergic projections from the MeA and BNST to the LS are important for individual recognition (De Vries et al., 1984; Mayes et al., 1988; Bluthe et al., 1990; Bluthe et al., 1993). Microinjections of Avp into the LS of normal or the Avp-deficient Brattleboro rat specifically facilitate social memory whereas Avpr1a antagonists or infusions of antisense Avpr1a oligonucleotides in normal rats impair it (Engelmann and Landgraf, 1994; Landgraf et al., 1995). Also, over-expression of vole Avpr1a within the LS of rats results in a prolonged ability to socially discriminate, 2 hours in experimental animals compared to 1 hour in controls (Landgraf et al., 2003).

The use of Avpr1a and Avpr1b KO mice has further elucidated the role of Avp in the formation of social memory. In the NIMH line of knockout mice the effects of Avpr1a (Hu et al., 2003) on social recognition have been mixed. Bielsky and colleagues (2004; 2005a) demonstrated that male Avpr1a −/− mice have impaired social recognition that can be rescued by over-expression of Avpr1a in the LS. On the other hand, Wersinger and colleagues (2007b) found no deficits in social recognition but rather a deficit in olfaction in Avpr1a −/−mice. Whether this discrepancy is due to slightly different strain backgrounds or testing procedures is unknown, but it is clear from previous work that Avp within the LS is important for social recognition. Interestingly, Avpr1b mice also show mild impairments in social recognition (Wersinger et al., 2002).

In female Avpr1a and Avpr1b KO mice, results consistent with those found by Wersinger and colleagues (2007a,b) have been found using a test of mate recognition. The Bruce effect is a pheromonally mediated response to chemosensory cues that results in a pregnancy termination when a recently mated female interacts with an unfamiliar male 24 hours after removal of the original mate (Bruce, 1959). As shown in Fig. 4, Avpr1a −/− females show a normal Bruce effect while Avpr1b −/− females fail to terminate their pregnancies in the presence of the unfamiliar male (Wersinger et al., 2007c). It is of interest to note that this represents one type of failure of the Bruce effect – Oxt KO mice display a second type in which the original mate is perceived as an unfamiliar male after 24 hours of separation (Fig. 4).

These findings, along with the observations in males, suggest that the Avpr1a may be more involved in the integration of main olfactory information, whereas the Avpr1b is involved in the formation and/or retrieval of memories associated with specific accessory olfactory cues and social encounters in order to generate appropriate behavioral responses (Wersinger et al., 2004). Given the abundance of Avpr1b in the hippocampal pyramidal cells of the CA2 region, the idea of a "social" cell in the hippocampus that would associate context (i.e., accessory olfactory cues) with the social experience, analogous to how CA1 pyramidal place cells associate visual input with direction and position in space (O'Keefe and Dostrovsky, 1971), is

plausible (Young et al., 2006). Future studies focusing on the contribution of Avpr1b to the social recognition will provide a more complete picture of the role of Avp in the formation of social memories. Fig. 5 illustrates the proposed roles for the Avpr1a and Avpr1b in the regulation of social behaviors.

2.3.2. Non-social memory—In addition to its effects on social memory and interactions, the pioneering work of David de Wied in the 1960s firmly established a modulatory effect of hypothalamic Avp on non-social learning and memory (see de Wied et al., 1993 for review). Beginning in 1965, de Wied found that removal of the posterior pituitary impaired active avoidance shuttlebox performance in rats (de Wied, 1965) that could be improved with Avp administration (Bohus et al., 1972). Since then, Avp has repeatedly been shown to affect non-spatial and spatial memory, with most studies finding an enhancing effect on memory, most likely through influences on the hippocampalseptal interactions (Croiset et al., 2000; see Table 2). The following section will describe a number of non-spatial and spatial tasks used to assess memory in rodents (for a full description of the tasks see Crawley, 2000)

2.3.2.1. Non-spatial learning and memory: Avp can enhance consolidation of memories, but seems more important in memory retrieval (Alescio-Lautier et al., 2000; Gulpinar and Yegen, 2004). Passive avoidance is often used to test Avp effects on non-spatial memory. In passive avoidance, animals receive a foot shock after entering a dark compartment, which they normally prefer over light spaces. At various times after this learning trial, retention of learning is tested by latency to enter the dark compartment (Laczi et al., 1983). Administration of Avp and two fragments (Avp_{4-8} and Avp_{5-9}) immediately after the last learning trial or just prior to the retention trial both improve passive avoidance learning (Kovacs et al., 1986). Recently, subcutaneous administration of NC-1900, an Avp_{4-9} analog with a longer half-life, was shown to ameliorate deficits in passive avoidance memory produced by inhibition of the COX-2 pathway (Sato et al., 2007), indicating that Avp may affect memory through this pathway. Moreover, administration of Avp fragments can affect memory up to 72 hours after training (Gaffori and De Wied, 1986), and even months after a single training trial (Izquierdo et al., 2002). Chronic treatment, as compared to acute treatment, with the Avp analog DDAVP is effective in aiding learning and retention of avoidance behavior (Hamburger-Bar et al., 1985). Endogenously, ‘good’ passive avoidance learners have significant decreases in Avp in the hippocampus, but not the amygdala, consistent with increased secretory activity in the hippocampus (Laczi et al., 1983). Conversely, administration of Avp antiserum into dorsal hippocampus and dentate gyrus significantly impair passive avoidance behavior (Kovacs et al., 1982). Thus, Avp activity in the hippocampus seems to improve memory for an aversive shock.

A second task often used is the “Go-No Go” visual discrimination task in which animals must learn to make a visual discrimination between two alleys, one of which always contains food reinforcement (Go trials) and the other never does (No Go trials). Learning is said to occur when running time decreases on the Go trial, and increases on the No Go trial (as if searching for food). Each session consists of twelve alternating trials; the first of each trial (Go and No Go) reflects retrieval of the learned memory, while the subsequent trials reflect relearning (Alescio-Lautier et al., 1995). On the Go-No Go task, intra-hippocampal Avp significantly improves retrieval and subsequent relearning when injected just prior to the retention trial (Alescio-Lautier and Soumireu-Mourat, 1998). Performance is better with injection into the ventral, as compared to the dorsal, hippocampus and only lesions to the ventral hippocampus blunt the effects of i.c.v. Avp (Alescio-Lautier and Soumireu-Mourat, 1998; Alescio-Lautier et al., 2000). Similarly, injection of Avp antiserum into the ventral, but not the dorsal, hippocampus prevents relearning of the Go-No Go task (Alescio-Lautier and Soumireu-Mourat, 1998). Finally, blockade of Avpr1a receptors impairs retrieval and relearning, even with subsequent Avp application (Alescio-Lautier et al., 1995).

2.3.2.2. Spatial learning: Spatial memory is memory of the spatial aspects of the surrounding environment. One of the oldest tests used for spatial memory is the radial arm maze in which food pellets are placed at the end of eight radiating arms. Optimal performance requires the animal visit each arm only once, and rodents quickly learn to do so by selecting unvisited arms (working memory) on the basis of their spatial location relative to extra-maze cues (in Packard and Ettenberg, 1985). Working memory in the radial arm maze is enhanced by Avp, as administration significantly enhances learned extinction behavior, i.e. learning that food was no longer present in the arms (Packard and Ettenberg, 1985). Avp_{4-9} also enhances working and reference memory on the radial arm maze (Dietrich and Allen, 1997a). Scopolamine, an anticholinergic, produces deficits in reference and working memory in the radial arm maze. These memory deficits are reversed with administration of Avp (Taga et al., 2001), Avp_{4-9} (Fujiwara et al., 1997; Mishima et al., 2001), and NC-1900 (Mishima et al., 2003).

Avp or its active fragments aid performance on other spatial memory tasks as well. In the hole board search task, animals receive a food reward in the same 4 (of 16) holes through multiple trials per day over many days. Reference memory consists of only going to those holes in which food has been found during the learning trials. Subcutaneous injection of Avp_{4-9} significantly improves reference memory and reduces the number of errors on this task (Vawter et al., 1997). The Hebb-Williams mazes consist of a battery of 12 mazes, and with moveable barriers the mazes can be made easy, moderate, or difficult (see Paban et al., 2003). Subcutaneous (s.c.), i.p., and dorsal hippocampal administration of Avp all significantly increase consolidation of a Hebb-Williams maze, but do not affect transfer of learning, i.e. learning times on a similarly-configured maze (Paban et al., 2003). Combined, the above studies indicate a general beneficial effect of Avp administration on spatial memory. Endogenous Avp is likely necessary for spatial memory performance, as animals with partial vasopressin insufficiency (Brattleboro heterozygotes: +/di) demonstrate poorer working memory than wildtype controls on a delayed-non-match-to-sample task in which the animal has to respond to an illuminated aperture different from the one on which it had been trained (Aarde and Jentsch, 2006).

Not all studies agree on the effect within the brain of Avp or its fragments on spatial memory. Early work found intra-septal administration of Avp significantly impairs learning of the Morris water maze (Engelmann et al., 1992). Injection of an Avpr1a antagonist suppressed the NC-1900 improvement on scopolamine-induced spatial memory deficits (Mishima et al., 2003), contrary to prior studies in which an Avpr1a antagonist did not impair performance on the radial arm maze (Dietrich and Allen, 1997a) or the Morris water maze (Everts and Koolhaas, 1999), in which an animal is trained to swim to a hidden escape platform using extra-maze spatial cues. However, Avpr1a KO mice have impaired working memory in the radial arm maze as compared to controls (Egashira et al., 2004; Egashira et al., 2006), indicating a role for the Avpr1a receptor in spatial task performance. Conversely, Avpr1b KO mice do not have impaired spatial memory on the Morris water maze (Wersinger et al., 2002; Egashira et al., 2004). Contrary to results of Paban et al (2003), i.c.v. injection of the active fragment Avp_{4-9} into the ventral, but not dorsal, hippocampus reverses scopolamine-induced spatial memory deficits (Fujiwara et al., 1997). Finally, Avp activity within the hippocampus seems necessary only for certain aspects of spatial memory, as rats with hippocampal lesions injected with Avp_{4-9} demonstrate deficits in working memory, but not reference memory, in the radial arm maze indicating effects outside of the hippocampus (Dietrich and Allen, 1997b). More study is needed to identify the receptor and its location in the brain upon which Avp acts to affect spatial memory.

2.3.2.3. Clinical studies: Some research indicates that Avp enhances human memory (Born et al., 1998). Early work has indicated a possible sexually-dimorphic effect of Avp, as an Avp analog improves memory for sentences (Beckwith et al., 1984; Beckwith et al., 1984) and enhances word recall (Pietrowsky et al., 1988) in males, but not females. Similarly, acute and

chronic Avp treatment in boys with learning disorders enhances memory of stories (Hamburger-Bar et al., 1987). As post-trial administration of an Avp analog does not enhance recall of passages, any effects of Avp on memory would be on acquisition only (Beckwith et al., 1995; see also Born et al., 1998).

Other studies indicate that Avp does not affect memory directly, but may enhance attention and arousal. DDAVP improves reaction times in males, but not memory itself (Beckwith et al., 1983). Avp in young and old subjects significantly elevates event-related potentials in the brain, which are associated with attentional mechanisms, but does not improve age-related cognitive impairments (Dodt et al., 1994). Similarly, repeated intranasal administration of Avp to healthy elderly persons does not significantly improve general long-term memory, although certain aspects of word recall are enhanced (Perras et al., 1997). Avp given to males does not affect consolidation of declarative memories, but there is a significant arousing effect of Avp as measured by electroencephalographic activity (Gais et al., 2002).

2.3.3. Conclusion—Administration of Avp agonists and antagonists, as well as data from Avpr1a and Avpr1b knockout mice, indicates a positive relationship between Avp and memory, both social and non-social. It is also possible that some of the effects of peripheral administration of Avp on behavior reflect changes in arousal, perhaps after an increase in blood pressure (see Koob et al., 1989, for review). Use of conditional knockouts for both the Avpr1a and Avpr1b are likely to be particularly useful in evaluating Avp's role in memory.

2.4. Stress, Anxiety and Depression

Anxiety and depression are behavioral states associated with stress. Pharmacological and transgenic studies in rodents allow the modeling of anxiety- and depression-related behaviors. In this section, the role of Avp and its two main receptors in the brain, Avpr1a and Avpr1b, will be discussed in relation to modulating anxiety and depression, as well as to actions on the HPA stress axis (see Table 2).

2.4.1. Anxiety—High densities of vasopressinergic fibers (De Vries and Buijs, 1983) and Avpr1a (Ostrowski et al., 1992) are found within the septum. Anxiety-related behavior, as measured on the elevated plus maze (EPM), is significantly reduced with septal infusion of antisense oligodeoxynucleotide to the Avpr1a mRNA (Landgraf et al., 1995), as well as with the Avpr1a antagonist $d(Ch_2)_5Tyr(Me)AVP$ (Liebsch et al., 1996; Engelmann et al., 2000), in the absence of altered locomotor activity. However, Appenrodt et al (1998) found both intraseptal and intraperitoneal (i.p.) application of Avp is also anxiolytic, indicating possible actions outside of the septum. Additionally, blocking Avpr1a in the septum via the antagonist $d(Ch_2)_5Tyr(Et)VAVP$ either fails to affect anxiety (Appenrodt et al., 1998) or increases anxiety (Everts and Koolhaas, 1999). Technical and antagonist differences may account for some of the differing results.

Some transgenic mice studies indicate a role for Avpr1a in modulating anxiety. Avpr1a KO males display significantly less anxiety-related behavior than wildtype males on a variety of tasks (Bielsky et al., 2004; Egashira et al., 2007). Additionally, over-expression of the Avpr1a gene in the LS significantly increases anxiety-related behavior (Bielsky et al., 2005a), further implicating Avpr1a in controlling the anxiety response. However, in another lab, no anxiolytic phenotype has been found in this line (Caldwell et al., 2006). Differences in strain background and technique may account for these differences. Interestingly, Avpr1a KO females do not display anxiolytic behaviors (Bielsky et al., 2005b; Caldwell et al., 2006). Sexual dimorphism in the extra-hypothalamic Avp system that ultimately projects to the septum (Wang et al., 1993) may underlie the lack of an Avp-related anxiety phenotype in Avpr1a KO females.

Current work has implicated oxytocin pathways in the amygdala as underlying anxiety in females (Amico et al., 2004).

Avp and Crh, both made in the PVN, synergize to increase release of ACTH from anterior pituitary corticotrophs (for review see Aguilera and Rabadan-Diehl, 2000b; Carrasco and Van de Kar, 2003). Avp release significantly increases in the PVN in response to acute (Wotjak et al., 1996) and chronic (Aguilera and Rabadan-Diehl, 2000b) stress. Stress can also increase Avpr1b in the pituitary (Aguilera et al., 1994; Aguilera and Rabadan-Diehl, 2000a,b). As expected, antagonism of Avpr1b reduces ACTH secretion (Serradeil-Le Gal et al., 2002b), and Avpr1b −/− mice have significantly lower ACTH and corticosterone levels compared to wildtype mice after certain insulin-induced hypoglycemic and restraint stresses (Lolait et al., 2007a).

The creation of an antagonist specific for the Avpr1b (SSR149415) has allowed greater analysis of the role Avpr1b plays in regulation of the stress response (see Serradeil-Le Gal et al., 2005 for review). Specifically, oral administration of SSR149415 prevents the Avp-induced rise in plasma ACTH levels, confirming a specific relationship between Avpr1b and the stress response (Serradeil-Le Gal et al., 2002b). Additionally, oral and i.p. administration of SSR149415 is anxiolytic in various classical (e.g., EPM) and atypical (mouse defensive test battery and social defeat) models of anxiety (Griebel et al., 2002; Serradeil-Le Gal et al., 2002b; Serradeil-Le Gal et al., 2003). Effects of hypophysectomy have been mixed; in one study, hypophysectomy did not alter the anxiolytic effects of the Avpr1b antagonist (Griebel et al., 2002), while in another study hypophysectomy blocked those effects (Shimazaki et al., 2006).

SSR149415 has no anxiolytic effects in either punished drinking behavior or exploration of the EPM when administered into the LS (Stemmelin et al., 2005). However, infusion of SSR149415 into the basolateral amygdala, but not central or medial nuclei, produces anxiolytic-like effects in performance on the EPM (Salome et al., 2006). All three nuclei contain Avpr1b receptors (Stemmelin et al., 2005) and likely mediate anxiety-related behaviors in both non-humans (Menard and Treit, 1999) and humans (Sheline et al., 1998).

Interestingly, Avpr1b −/− males do not have an anxiolytic phenotype (Wersinger et al., 2002; Caldwell et al., 2006). The normal catecholamine release in response to stress is decreased in Avpr1b −/− males, particularly release of epinephrine (Itoh et al., 2006). As noted above, no differences in circulating ACTH and corticosterone levels between Avpr1b KO and wildtype mice have been found (Wersinger et al., 2002; Lolait et al., 2007a). Using the resident-intruder paradigm, stress-induced changes in corticosterone did not differ between Avpr1b KO and wildtype mice (Wersinger et al., 2002). However, after chronic, but not acute, restraint stress, significantly less ACTH is released in Avpr1b −/− mice as compared to wildtype mice (Lolait et al., 2007a). Furthermore, acute insulin-induced hypoglycemic stress and acute ethanol or lipopolysaccharide administration elevate both ACTH and corticosterone to lesser extents in the Avpr1b KO (Lolait et al., 2007a; Lolait et al., 2007b). These studies indicate that Avpr1b contributes to normal stress responses in a context-dependent manner.

2.4.2. Trait-dependent anxiety—Rats bred for high or low anxiety (HAB and LAB, respectively) provide an animal model for studying the relationship between abnormal HPA activity and neuroendocrine regulatory factors. HAB rats display greater depressive- and anxiety-like behaviors that are accompanied by enhanced stress-induced secretion of ACTH and corticosterone than LAB rats (Landgraf et al., 1999; Landgraf, 2006). The HPA axis of male HAB rats is incompletely suppressed by the synthetic corticosteroid dexamethasone (DEX): treatment with Crh after DEX pretreatment stimulates ACTH secretion, indicating abnormal HPA activation (Keck et al., 2002). Additionally, Avp is significantly elevated and

released within the PVN of the hypothalamus in HAB, but not LAB, male rats, both with (Keck et al., 2002) and without stress (Wigger et al., 2004; Bosch et al., 2006). Administration of the Avpr1a antagonist d(Ch_2)$_5$Tyr(Me)AVP suppresses the ACTH secretion normally seen in HAB rats in response to DEX/Crh administration (Keck et al., 2002), as well as decreases anxiety- and depression-related behaviors (Wigger et al., 2004). Interestingly, prenatal stress increases Avp mRNA expression in the PVN of LAB rats and subsequent anxiety in the EPM and hole-board tests of anxiety (Bosch et al., 2006).

Single nucleotide polymorphisms (SNPs) have been studied as potential causes of the different HAB and LAB phenotypes (Murgatroyd et al., 2004; Landgraf et al., 2007). One specific SNP [A(-1276)G] results in reduced binding of the transcriptional repressor CArG binding factor A (CBF-A), which is highly co-expressed in Avp-containing neurons in the PVN (Murgatroyd et al., 2004). Reduction of CBF-A binding causes increased transcription of Avp in the PVN of HAB animals and, perhaps, the subsequent high-anxiety phenotype. Conversely, an SNP leading to an amino acid change in the signal peptide of Avp may lead to the decrease in Avp in the LAB rats (see Landgraf, 2006; Landgraf et al., 2007 for review).

2.4.3. Depression—Ample evidence indicates that, in addition to affecting anxiety-related behavior, Avp affects depression-related behavior. In rodents, the forced swim task produces immobility that can be countered with antidepressants (Porsolt et al., 1977; West and Weiss, 2005). Acute forced swimming induces a significant increase in Avp release in both the SON and PVN that increases further in the PVN with repeated swimming (Wotjak et al., 1998). Similarly, training in the Morris water maze for three days significantly increases release of Avp in the PVN after each test session, and Avp release tends to rise each day (Engelmann et al., 2006). Forced swim stress also increases Avp release in the mediolateral and ventral septum (Ebner et al., 1999), the amygdala (Ebner et al., 2002), and the SCN (Engelmann et al., 1998). Brattleboro rats show less immobility on the forced swim task (Mlynarik et al., 2007). Forced swimming does not elevate plasma Avp levels, indicating dissociation between central and peripheral Avp release with an applied stressor (Wotjak et al., 1998).

Applications of the Avpr1a antagonist d(Ch_2)$_5$Tyr(Me)AVP into both the mediolateral septum and the amygdala have antidepressant-like effects (Ebner et al., 1999; Ebner et al., 2002). Antidepressant-like effects are observed with oral and i.p. administration of the Avpr1b antagonist SSR149415, even after hypophysectomy (Griebel et al., 2002). Infusion of SSR149415 into the LS (Stemmelin et al., 2005) and into three nuclei of the amygdala also decreases immobility time in the forced swim task (Salome et al., 2006). Finally, ACTH increases after forced swim in wildtype, but not Avpr1b KO, mice (Tanoue et al., 2004). However, wildtype, Avpr1a −/− and Avpr1b −/− mice do not differ in this swimming behavior (Bielsky et al., 2004; Tanoue et al., 2004; Caldwell et al., 2006; Egashira et al., 2007). Nevertheless, Avpr1b in general appears to modulate depression-related behaviors and their associated HPA responses.

2.4.4. Clinical studies—A large body of evidence indicates involvement of Avp in human stress-related diseases, such as anxiety disorders and major depression. Gold et al (1978) were the first to propose a role for vasopressin in mood disorders; studies since then have upheld this idea. Patients with major depression have significantly elevated plasma Avp compared to healthy controls (van Londen et al., 1997), as well as elevated ACTH and cortisol levels after Avp administration (Dinan et al., 2004). An increase in Avp mRNA in the SON of depressed patients compared with controls could explain the elevated plasma Avp levels (Meynen et al., 2006). Interestingly, depressed patients with the melancholic subtype have significantly greater Avp mRNA in both SON and PVN, indicating the increase in Avp may be more pronounced with this type of depression (Meynen et al., 2006). Similarly, depressed patients who attempted or committed suicide have higher plasma Avp (Inder et al., 1997) or Avp-ir neurons in the PVN

(Merali et al., 2006), respectively, than depressed patients who did not. Thus, higher Avp expression in the hypothalamus may be associated with more severe types and symptoms of depression, reflected in alteration of the HPA axis (for review, see Landgraf, 2006).

The likelihood of developing a mood disorder increases with a family history of the disease (Sullivan et al., 2000). A recent study indicates that above-normal plasma Avp (relative to healthy controls) is highly correlated to higher anxiety and psychomotor retardation levels, and is associated with family history of depression (Goekoop et al., 2006). Additionally, an SNP in the Avpr1b gene may protect against development of major depression, as it is significantly over-represented in healthy controls as compared to depressed patients (van West et al., 2004). Thus, a fair amount of evidence exists to implicate Avp in anxiety and depression.

2.4.5. Conclusion—Avp, particularly within the LS, seems to aid in the regulation of anxiety- and depression-related behavior. However, the precise contributions of each Avp receptor remain unclear, in part due to differing results using receptor antagonists and transgenic mice. Ample evidence exists indicating a role for Avp in regulation of the HPA axis in both rodents and humans, which could account for some of the anxiolytic or antidepressant effects of decreased Avp. Future studies using conditional knockouts of the Avpr1a and Avpr1b will allow for greater insight into the relationship between Avp and stress-related states.

3. Implications for Human Behavior

Many of the defining characteristics of autism spectrum disorders (ASD) such as atypical social behavior, repetitive and stereotypic behavioral patterns, and increased anxiety and emotionality (for review see Baron-Cohen and Belmonte, 2005; Lord et al., 2000), are affected by Avp. Interestingly, ASD are more prevalent in males (Fombonne, 2003; Chakrabarti and Fombonne, 2005); likewise the effects of Avp on these behaviors are most pronounced in male animals (Bluthe et al., 1990; Bielsky et al., 2005b; for review see Carter, 2007). While the above observations may simply be correlative, there have been a few studies of human sibling pairs (only one affected) and child-parents trios hinting that the *Avpr1a* is an autism susceptibility gene (Kim et al., 2002; Wassink et al., 2004; Yirmiya et al., 2006). A more powerful approach using more extended families found a significant linkage to chromosome 112q14 where, among other genes, the Avpr1a gene is located (Ma et al., 2007). While the 5′ flanking region of the *Avpr1a* is not thought to cause autism, because ASD likely has diverse etiologies (Muller, 2007; Sebat et al., 2007; Yang and Gill, 2007), it has been proposed that its variation could contribute, along with other genetic and environmental factors, to affect the onset and severity of the disease (for review see Hammock and Young, 2006; Carter, 2007).

The microsatellite sequences of the 5′ flanking region of the *Avpr1a* have been examined for their influences on various behaviors. A very strong linkage to creativity in dance was found by Bachner-Melman et al. (2005), with a weaker correlation between the microsatellite sequences and eating behavior (Bachner-Melman et al., 2004), and none for hypersexuality (Geller et al., 2005). These linkage studies, taken together, suggest a possible role for these polymorphic microsatellites in influencing Avpr1a's role in social communication and/or the interpretation of social context. Also, as noted above, a particular SNP in the *Avpr1b* is associated with reduced susceptibility to recurrent major depression (van West et al., 2004). These genetic approaches, coupled with the development of better behavioral animal models, suggest that the next decade should be a rewarding one for investigators of Avp.

Acknowledgements

This work was supported by the NIMH Intramural Research Program (Z01-MH-002498-17).

Abbreviations

ACTH, adrenocorticotropic hormone
AH, anterior hypothalamus
Avp, arginine vasopressin
ASD, autism spectrum disorders
BNST, bed nucleus of the stria terminalis
CNS, central nervous system
CSF, cerebrospinal fluid
Crh, corticotrophin releasing hormone
DDAVP, Desmopressin
DEX, dexamethasone
HPA, hypothalamic-pituitary-adrenal
ir, immunoreactive
IGR, intergenic region
i.c.v., intracerebroventricular
i.p., intraperitoneal
KO, −/−, knockout
LS, lateral septum
MeA, medial amygdala
MPOA-AH, medial preoptic-anterior hypothalamic area
Oxt, oxytocin
Oxtr, oxytocin receptor
PVN, paraventricular nucleus
5-HT, serotonin
SNPs, Single nucleotide polymorphisms
SCN, suprachiasmatic nucleus
SON, supraoptic nucleus
Avpr1a, vasopressin 1a receptor
Avpr1b, vasopressin 1b receptor
Avpr2, vasopressin 2 receptor

References

Aarde SM, Jentsch JD. Haploinsufficiency of the arginine-vasopressin gene is associated with poor spatial working memory performance in rats. Horm Behav 2006;49:501–508. [PubMed: 16375903]

Acher R. Structure evolution and processing adaptation of neurohypophysial hormone-neurophysin precursors. Prog Clin Biol Res 1990;342:1–9. [PubMed: 2199989]

Aguilera G, Pham Q, Rabadan-Diehl C. Regulation of pituitary vasopressin receptors during chronic stress: relationship to corticotroph responsiveness. J Neuroendocrinol 1994;6:299–304. [PubMed: 7612075]

Aguilera G, Rabadan-Diehl C. Regulation of vasopressin V1b receptors in the anterior pituitary gland of the rat. Exp Physiol 2000a;85:19S–26S. [PubMed: 10795903]Spec No

Aguilera G, Rabadan-Diehl C. Vasopressinergic regulation of the hypothalamic-pituitary-adrenal axis: implications for stress adaptation. Regul Pept 2000b;96:23–29. [PubMed: 11102648]

Albers HE, Dean A, Karom MC, Smith D, Huhman KL. Role of V1a vasopressin receptors in the control of aggression in Syrian hamsters. Brain Res 2006;1073-1074:425–430. [PubMed: 16445890]

Albers HE, Liou SY, Ferris CF. Testosterone alters the behavioral response of the medial preoptic-anterior hypothalamus to microinjection of arginine vasopressin in the hamster. Brain Res 1988;456:382–386. [PubMed: 3208086]

Albers HE, Rowland CM, Ferris CF. Arginine-vasopressin immunoreactivity is not altered by photoperiod or gonadal hormones in the Syrian hamster (Mesocricetus auratus). Brain Res 1991;539:137–142. [PubMed: 2015498]

Albrecht U, Eichele G. The mammalian circadian clock. Curr Opin Genet Dev 2003;13:271–277. [PubMed: 12787789]

Alescio-Lautier B, Paban V, Soumireu-Mourat B. Neuromodulation of memory in the hippocampus by vasopressin. Eur J Pharmacol 2000;405:63–72. [PubMed: 11033315]

Alescio-Lautier B, Rao H, Paban V, Devigne C, Soumireu-Mourat B. Inhibition of the vasopressin-enhancing effect on memory retrieval and relearning by a vasopressin V1 receptor antagonist in mice. Eur J Pharmacol 1995;294:763–770. [PubMed: 8750743]

Alescio-Lautier B, Soumireu-Mourat B. Role of vasopressin in learning and memory in the hippocampus. Prog Brain Res 1998;119:501–521. [PubMed: 10074809]

Alves SE, Lopez V, McEwen BS, Weiland NG. Differential colocalization of estrogen receptor beta (ERbeta) with oxytocin and vasopressin in the paraventricular and supraoptic nuclei of the female rat brain: an immunocytochemical study. Proc Natl Acad Sci U S A 1998;95:3281–3286. [PubMed: 9501254]

Amico JA, Mantella RC, Vollmer RR, Li X. Anxiety and stress responses in female oxytocin deficient mice. J Neuroendocrinol 2004;16:319–324. [PubMed: 15089969]

Antoni FA. Novel ligand specificity of pituitary vasopressin receptors in the rat. Neuroendocrinology 1984;39:186–188. [PubMed: 6089020]

Antoni FA, Chadio SE. Essential role of magnesium in oxytocin-receptor affinity and ligand specificity. Biochem J 1989;257:611–614. [PubMed: 2539090]

Aoyagi T, Birumachi JI, Hiroyama M, Fujiwara Y, Sanbe A, et al. Alteration of glucose homeostasis in V1a vasopressin receptor-deficient mice. Endocrinology. 2007[Epub Feb 15]

Appenrodt E, Schnabel R, Schwarzberg H. Vasopressin administration modulates anxiety-related behavior in rats. Physiol Behav 1998;64:543–547. [PubMed: 9761230]

Aragona BJ, Liu Y, Curtis JT, Stephan FK, Wang Z. A critical role for nucleus accumbens dopamine in partner-preference formation in male prairie voles. J Neurosci 2003;23:3483–3490. [PubMed: 12716957]

Aragona BJ, Liu Y, Yu YJ, Curtis JT, Detwiler JM, et al. Nucleus accumbens dopamine differentially mediates the formation and maintenance of monogamous pair bonds. Nat Neurosci 2006;9:133–139. [PubMed: 16327783]

Aragona BJ, Wang Z. The prairie vole (Microtus ochrogaster): an animal model for behavioral neuroendocrine research on pair bonding. Ilar J 2004;45:35–45. [PubMed: 14752206]

Archer R, du Vigneaud V. La structure de la vasopressin de boeuf. Biochim Acta (Amst) 1953;12:487–488.

Askew A, Gonzalez FA, Stahl JM, Karom MC. Food competition and social experience effects on V1a receptor binding in the forebrain of male Long-Evans hooded rats. Horm Behav 2006;49:328–336. [PubMed: 16154572]

Bachner-Melman R, Dina C, Zohar AH, Constantini N, Lerer E, et al. AVPR1a and SLC6A4 gene polymorphisms are associated with creative dance performance. PLoS Genet 2005;1:e42. [PubMed: 16205790]

Bachner-Melman R, Zohar AH, Elizur Y, Nemanov L, Gritsenko I, et al. Association between a vasopressin receptor AVPR1A promoter region microsatellite and eating behavior measured by a self-report questionnaire (Eating Attitudes Test) in a family-based study of a nonclinical population. Int J Eat Disord 2004;36:451–460. [PubMed: 15558634]

Bales KL, Kim AJ, Lewis-Reese AD, Sue Carter C. Both oxytocin and vasopressin may influence alloparental behavior in male prairie voles. Horm Behav 2004;45:354–361. [PubMed: 15109910]

Bamshad M, Novak MA, de Vries GJ. Cohabitation alters vasopressin innervation and paternal behavior in prairie voles (Microtus ochrogaster). Physiol Behav 1994;56:751–758. [PubMed: 7800744]

Bankir L. Antidiuretic action of vasopressin: quantitative aspects and interaction between V1a and V2 receptor-mediated effects. Cardiovasc Res 2001;51:372–390. [PubMed: 11476728]

Barberis C, Morin D, Durroux T, Mouillac B, Guillon G, et al. Molecular pharmacology of AVP and OT receptors and therapeutic potential. Drug News Perspect 1999;12:279–292.

Baron-Cohen S, Belmonte MK. Autism: a window onto the development of the social and the analytic brain. Annu Rev Neurosci 2005;28:109–126. [PubMed: 16033325]

Barreca T, Franceschini R, Siani C, Messina V, Francaviglia N, et al. Diurnal pattern of plasma and cerebrospinal-fluid vasopressin levels in hydrocephalic patients: absence of a circadian rhythm and of a correlation between plasma and cerebrospinal-fluid variations. Horm Res 1988;30:28–31. [PubMed: 3220462]

Beckwith BE, Couk DI, Till TS. Vasopressin analog influences the performance of males on a reaction time task. Peptides 1983;4:707–709. [PubMed: 6657514]

Beckwith BE, Petros TV, Bergloff PJ, Swenson RR, Paulson R. Failure of posttrial administration of vasopressin analogue (DDAVP) to influence memory in healthy, young, male volunteers. Peptides 1995;16:1327–1328. [PubMed: 8745039]

Beckwith BE, Till RE, Schneider V. Vasopressin analog (DDAVP) improves memory in human males. Peptides 1984;5:819–822. [PubMed: 6494028]

Bester-Meredith JK, Marler CA. Vasopressin and aggression in cross-fostered California mice (Peromyscus californicus) and white-footed mice (Peromyscus leucopus). Horm Behav 2001;40:51–64. [PubMed: 11467884]

Bester-Meredith JK, Marler CA. Vasopressin and the transmission of paternal behavior across generations in mated, cross-fostered Peromyscus mice. Behav Neurosci 2003;117:455–463. [PubMed: 12802874]

Bester-Meredith JK, Martin PA, Marler CA. Manipulations of vasopressin alter aggression differently across testing conditions in monogamous and non-monogamous *Peromyscus* mice. Aggressive Behavior 2005;31

Bester-Meredith JK, Young LJ, Marler CA. Species differences in paternal behavior and aggression in peromyscus and their associations with vasopressin immunoreactivity and receptors. Horm Behav 1999;36:25–38. [PubMed: 10433884]

Bielsky IF, Hu SB, Ren X, Terwilliger EF, Young LJ. The V1a vasopressin receptor is necessary and sufficient for normal social recognition: a gene replacement study. Neuron 2005a;47:503–513. [PubMed: 16102534]

Bielsky IF, Hu SB, Szegda KL, Westphal H, Young LJ. Profound impairment in social recognition and reduction in anxiety-like behavior in vasopressin V1a receptor knockout mice. Neuropsychopharmacology 2004;29:483–493. [PubMed: 14647484]

Bielsky IF, Hu SB, Young LJ. Sexual dimorphism in the vasopressin system: lack of an altered behavioral phenotype in female V1a receptor knockout mice. Behav Brain Res 2005b;164:132–136. [PubMed: 16046007]

Blanchard RJ, Griebel G, Farrokhi C, Markham C, Yang M, et al. AVP V1b selective antagonist SSR149415 blocks aggressive behaviors in hamsters. Pharmacol Biochem Behav 2005;80:189–194. [PubMed: 15652395]

Blanchard RJ, Wall PM, Blanchard DC. Problems in the study of rodent aggression. Horm Behav 2003;44:161–170. [PubMed: 14609538]

Bluthe RM, Gheusi G, Dantzer R. Gonadal steroids influence the involvement of arginine vasopressin in social recognition in mice. Psychoneuroendocrinology 1993;18:323–335. [PubMed: 8316618]

Bluthe RM, Schoenen J, Dantzer R. Androgen-dependent vasopressinergic neurons are involved in social recognition in rats. Brain Res 1990;519:150–157. [PubMed: 1975762]

Bohus B, Ader R, de Wied D. Effects of vasopressin on active and passive avoidance behavior. Horm Behav 1972;3:191–197. [PubMed: 4680509]

Bohus B, de Wied D. The vasopressin deficient Brattleboro rats: a natural knockout model used in the search for CNS effects of vasopressin. Prog Brain Res 1998;119:555–573. [PubMed: 10074812]

Born J, Lange T, Kern W, McGregor GP, Bickel U, et al. Sniffing neuropeptides: a transnasal approach to the human brain. Nat Neurosci 2002;5:514–516. [PubMed: 11992114]

Born J, Pietrowsky R, Fehm HL. Neuropsychological effects of vasopressin in healthy humans. Prog Brain Res 1998;119:619–643. [PubMed: 10074814]

Bosch OJ, Kromer SA, Neumann ID. Prenatal stress: opposite effects on anxiety and hypothalamic expression of vasopressin and corticotropin-releasing hormone in rats selectively bred for high and low anxiety. Eur J Neurosci 2006;23:541–551. [PubMed: 16420461]

Brownstein MJ, Russell JT, Gainer H. Synthesis, transport, and release of posterior pituitary hormones. Science 1980;207:373–378. [PubMed: 6153132]

Bruce HM. An exteroceptive block to pregnancy in the mouse. Nature 1959;184:105. [PubMed: 13805128]

Buijs RM, Swaab DF, Dogterom J, van Leeuwen FW. Intra- and extrahypothalamic vasopressin and oxytocin pathways in the rat. Cell Tissue Res 1978;186:423–433. [PubMed: 342106]

Buijs RM, van Eden CG, Goncharuk VD, Kalsbeek A. The biological clock tunes the organs of the body: timing by hormones and the autonomic nervous system. J Endocrinol 2003;177:17–26. [PubMed: 12697033]

Buijs RM, Wortel J, Van Heerikhuize JJ, Feenstra MG, Ter Horst GJ, et al. Anatomical and functional demonstration of a multisynaptic suprachiasmatic nucleus adrenal (cortex) pathway. Eur J Neurosci 1999;11:1535–1544. [PubMed: 10215906]

Burbach JP, Luckman SM, Murphy D, Gainer H. Gene regulation in the magnocellular hypothalamo-neurohypophysial system. Physiol Rev 2001;81:1197–1267. [PubMed: 11427695]

Caba M, Silver R, Gonzalez-Mariscal G, Jimenez A, Beyer C. Oxytocin and vasopressin immunoreactivity in rabbit hypothalamus during estrus, late pregnancy, and postpartum. Brain Res 1996;720:7–16. [PubMed: 8782891]

Caffe AR, van Leeuwen FW, Luiten PG. Vasopressin cells in the medial amygdala of the rat project to the lateral septum and ventral hippocampus. J Comp Neurol 1987;261:237–252. [PubMed: 3305600]

Caldwell HK, Albers HE. Short-photoperiod exposure reduces vasopressin (V1a) receptor binding but not arginine-vasopressin-induced flank marking in male Syrian hamsters. J Neuroendocrinol 2003;15:971–977. [PubMed: 12969242]

Caldwell HK, Albers HE. Photoperiodic regulation of vasopressin receptor binding in female Syrian hamsters. Brain Res 2004a;1002:136–141. [PubMed: 14988043]

Caldwell HK, Albers HE. Effect of photoperiod on vasopressin-induced aggression in Syrian hamsters. Horm Behav 2004b;46:444–449. [PubMed: 15465530]

Caldwell HK, Stewart J, Wiedholz LM, Millstein RA, Iacangelo A, et al. The acute intoxicating effects of ethanol are not dependent on the vasopressin 1a or 1b receptors. Neuropeptides 2006;40:325–337. [PubMed: 17049983]

Caldwell, HK.; Young, WS, 3rd. Oxytocin and Vasopressin: Genetics and Behavioral Impolications. In: Lim, R., editor. Neuroactive Proteins and Peptides. New York; Springer: 2006. p. 573-607.

Caldwell JD, Greer ER, Johnson MF, Prange AJ Jr. Pedersen CA. Oxytocin and vasopressin immunoreactivity in hypothalamic and extrahypothalamic sites in late pregnant and postpartum rats. Neuroendocrinology 1987;46:39–47. [PubMed: 3614554]

Carrasco GA, Van de Kar LD. Neuroendocrine pharmacology of stress. Eur J Pharmacol 2003;463:235–272. [PubMed: 12600714]

Carter CS. Neuroendocrine perspectives on social attachment and love. Psychoneuroendocrinology 1998;23:779–818. [PubMed: 9924738]

Carter CS. Sex differences in oxytocin and vasopressin: implications for autism spectrum disorders? Behav Brain Res 2007;176:170–186. [PubMed: 17000015]

Carter CS, DeVries AC, Getz LL. Physiological substrates of mammalian monogamy: the prairie vole model. Neurosci Biobehav Rev 1995;19:303–314. [PubMed: 7630584]

Carter CS, Getz LL. Monogamy and the prairie vole. Sci Am 1993;268:100–106. [PubMed: 8516669]

Chakrabarti S, Fombonne E. Pervasive developmental disorders in preschool children: confirmation of high prevalence. Am J Psychiatry 2005;162:1133–1141. [PubMed: 15930062]

Chan WY, Wo NC, Stoev ST, Cheng LL, Manning M. Discovery and design of novel and selective vasopressin and oxytocin agonists and antagonists: the role of bioassays. Exp Physiol 2000;85:7S–18S. [PubMed: 10795902]Spec No

Cho MM, DeVries AC, Williams JR, Carter CS. The effects of oxytocin and vasopressin on partner preferences in male and female prairie voles (Microtus ochrogaster). Behav Neurosci 1999;113:1071–1079. [PubMed: 10571489]

Coccaro EF, Kavoussi RJ, Hauger RL, Cooper TB, Ferris CF. Cerebrospinal fluid vasopressin levels: correlates with aggression and serotonin function in personality-disordered subjects. Arch Gen Psychiatry 1998;55:708–714. [PubMed: 9707381]

Compaan JC, Buijs RM, Pool CW, De Ruiter AJ, Koolhaas JM. Differential lateral septal vasopressin innervation in aggressive and nonaggressive male mice. Brain Res Bull 1993;30:1–6. [PubMed: 8420617]

Cooper MA, Karom M, Huhman KL, Albers HE. Repeated agonistic encounters in hamsters modulate AVP V1a receptor binding. Horm Behav 2005;48:545–551. [PubMed: 15935353]

Crawley, JN. What's Wrong With My Mouse: Behavioral phenotypine of transgenic and knockout mice. Wiley-Liss; New York: 2000.

Croiset G, Nijsen MJ, Kamphuis PJ. Role of corticotropin-releasing factor, vasopressin and the autonomic nervous system in learning and memory. Eur J Pharmacol 2000;405:225–234. [PubMed: 11033330]

Crowley RS, Amico JA. Gonadal steroid modulation of oxytocin and vasopressin gene expression in the hypothalamus of the osmotically stimulated rat. Endocrinology 1993;133:2711–2718. [PubMed: 8243294]

Dantzer R, Bluthe RM, Koob GF, Le Moal M. Modulation of social memory in male rats by neurohypophyseal peptides. Psychopharmacology (Berl) 1987;91:363–368. [PubMed: 3104959]

De Vries GJ, Best W, Sluiter AA. The influence of androgens on the development of a sex difference in the vasopressinergic innervation of the rat lateral septum. Brain Res 1983;284:377–380. [PubMed: 6871731]

De Vries GJ, Buijs RM. The origin of the vasopressinergic and oxytocinergic innervation of the rat brain with special reference to the lateral septum. Brain Res 1983;273:307–317. [PubMed: 6311351]

De Vries GJ, Buijs RM, Sluiter AA. Gonadal hormone actions on the morphology of the vasopressinergic innervation of the adult rat brain. Brain Res 1984;298:141–145. [PubMed: 6722551]

De Vries GJ, Buijs RM, Van Leeuwen FW, Caffe AR, Swaab DF. The vasopressinergic innervation of the brain in normal and castrated rats. J Comp Neurol 1985;233:236–254. [PubMed: 3882778]

De Vries GJ, Miller MA. Anatomy and function of extrahypothalamic vasopressin systems in the brain. Prog Brain Res 1998;119:3–20. [PubMed: 10074777]

de Wied D. The influence of the posterior and intermediate lobe of the pituitary and pituitary peptides on the maintenance of a conditioned avoidance response in rats. Int J Neuropharmacol 1965;16

de Wied D, Diamant M, Fodor M. Central nervous system effects of the neurohypophyseal hormones and related peptides. Front Neuroendocrinol 1993;14:251–302. [PubMed: 8258377]

Delville Y, Conklin LS, Ferris CF. Differential expression of vasopressin receptor binding in the hypothalamus during lactation in golden hamsters. Brain Res 1995;689:147–150. [PubMed: 8528699]

Delville Y, De Vries GJ, Schwartz WJ, Ferris CF. Flank-marking behavior and the neural distribution of vasopressin innervation in golden hamsters with suprachiasmatic lesions. Behav Neurosci 1998;112:1486–1501. [PubMed: 9926831]

Delville Y, Mansour KM, Ferris CF. Serotonin blocks vasopressin-facilitated offensive aggression: interactions within the ventrolateral hypothalamus of golden hamsters. Physiol Behav 1996a;59:813–816. [PubMed: 8778871]

Delville Y, Mansour KM, Ferris CF. Testosterone facilitates aggression by modulating vasopressin receptors in the hypothalamus. Physiol Behav 1996b;60:25–29. [PubMed: 8804638]

Dietrich A, Allen JD. Vasopressin and memory. I. The vasopressin analogue AVP4-9 enhances working memory as well as reference memory in the radial arm maze. Behav Brain Res 1997a;87:195–200. [PubMed: 9331487]

Dietrich A, Allen JD. Vasopressin and memory. II. Lesions to the hippocampus block the memory enhancing effects of AVP4-9 in the radial maze. Behav Brain Res 1997b;87:201–208. [PubMed: 9331488]

Dinan TG, O'Brien S, Lavelle E, Scott LV. Further neuroendocrine evidence of enhanced vasopressin V3 receptor responses in melancholic depression. Psychol Med 2004;34:169–172. [PubMed: 14971638]

Dodt C, Pietrowsky R, Sewing A, Zabel A, Fehm HL, et al. Effects of vasopressin on event-related potential indicators of cognitive stimulus processing in young and old humans. J Gerontol 1994;49:M183–188. [PubMed: 8014393]

du Vigneaud, V. A trail of research. Cornell University Press; Ithaca: 1952.

du Vigneaud V, Gish DT, Katsoyannis PG. A synthetic preparation possessing biological properties associated with arginine-vasopressin. J Am Chem Soc 1954a;76:4751–4752.

du Vigneaud V, Lawler HC, Popenoe EA. Enzymic cleavage of glycinamide from vasopressin and a proposed structure for this pressor-antidiuretic hormone of the posterior pituitary. J Am Chem Soc 1953a;75:4880–4881.

du Vigneaud V, Ressler C, Swan JM, Roberts CW, Katsoyannis PG. The synthesis of oxytocin. J Am Chem Soc 1954b;76:3115–3121.

du Vigneaud V, Ressler C, Trippett S. The sequence of amino acids in oxytocin, with a proposal for the structure of oxytocin. J Biol Chem 1953b;205:949–957. [PubMed: 13129273]

Dubois-Dauphin M, Theler JM, Ouarour A, Pevet P, Barberis C, et al. Regional differences in testosterone effects on vasopressin receptors and on vasopressin immunoreactivity in intact and castrated Siberian hamsters. Brain Res 1994;638:267–276. [PubMed: 8199865]

Ebner K, Wotjak CT, Holsboer F, Landgraf R, Engelmann M. Vasopressin released within the septal brain area during swim stress modulates the behavioural stress response in rats. Eur J Neurosci 1999;11:997–1002. [PubMed: 10103093]

Ebner K, Wotjak CT, Landgraf R, Engelmann M. Forced swimming triggers vasopressin release within the amygdala to modulate stress-coping strategies in rats. Eur J Neurosci 2002;15:384–388. [PubMed: 11849304]

Egashira N, Tanoue A, Higashihara F, Mishima K, Fukue Y, et al. V1a receptor knockout mice exhibit impairment of spatial memory in an eight-arm radial maze. Neurosci Lett 2004;356:195–198. [PubMed: 15036628]

Egashira N, Tanoue A, Matsuda T, Koushi E, Harada S, et al. Impaired social interaction and reduced anxiety-related behavior in vasopressin V1a receptor knockout mice. Behav Brain Res 2007;178:123–127. [PubMed: 17227684]

Egashira N, Tanoue A, Tsujimoto G, Mishima K, Takano Y, et al. [Vasopressin receptor knockout mice as an animal model of psychiatric disorders]. Nihon Shinkei Seishin Yakurigaku Zasshi 2006;26:101–105. [PubMed: 16722468]

Engelmann M, Bures J, Landgraf R. Vasopressin administration via microdialysis into the septum interferes with the acquisition of spatial memory in rats. Neurosci Lett 1992;142:69–72. [PubMed: 1407722]

Engelmann M, Ebner K, Landgraf R, Wotjak CT. Swim stress triggers the release of vasopressin within the suprachiasmatic nucleus of male rats. Brain Res 1998;792:343–347. [PubMed: 9593985]

Engelmann M, Ebner K, Landgraf R, Wotjak CT. Effects of Morris water maze testing on the neuroendocrine stress response and intrahypothalamic release of vasopressin and oxytocin in the rat. Horm Behav 2006;50:496–501. [PubMed: 16875693]

Engelmann M, Landgraf R. Microdialysis administration of vasopressin into the septum improves social recognition in Brattleboro rats. Physiol Behav 1994;55:145–149. [PubMed: 8140159]

Engelmann M, Wotjak CT, Ebner K, Landgraf R. Behavioural impact of intraseptally released vasopressin and oxytocin in rats. Exp Physiol 2000;85:125S–130S. [PubMed: 10795914]Spec No

Everts HG, De Ruiter AJ, Koolhaas JM. Differential lateral septal vasopressin in wild-type rats: correlation with aggression. Horm Behav 1997;31:136–144. [PubMed: 9154434]

Everts HG, Koolhaas JM. Differential modulation of lateral septal vasopressin receptor blockade in spatial learning, social recognition, and anxiety-related behaviors in rats. Behav Brain Res 1999;99:7–16. [PubMed: 10512567]

Farini F. Diabete insipido ed opoterapia. Gazz Osped Clin 1913;34:1135–1139.

Ferris CF, Albers HE, Wesolowski SM, Goldman BD, Luman SE. Vasopressin injected into the hypothalamus triggers a stereotypic behavior in golden hamsters. Science 1984;224:521–523. [PubMed: 6538700]

Ferris CF, Axelson JF, Martin AM, Roberge LF. Vasopressin immunoreactivity in the anterior hypothalamus is altered during the establishment of dominant/subordinate relationships between hamsters. Neuroscience 1989;29:675–683. [PubMed: 2739905]

Ferris CF, Delville Y, Grzonka Z, Luber-Narod J, Insel TR. An iodinated vasopressin (V1) antagonist blocks flank marking and selectively labels neural binding sites in golden hamsters. Physiol Behav 1993;54:737–747. [PubMed: 8248352]

Ferris CF, Lu SF, Messenger T, Guillon CD, Heindel N, et al. Orally active vasopressin V1a receptor antagonist, SRX251, selectively blocks aggressive behavior. Pharmacol Biochem Behav 2006;83:169–174. [PubMed: 16504276]

Ferris CF, Meenan DM, Axelson JF, Albers HE. A vasopressin antagonist can reverse dominant/subordinate behavior in hamsters. Physiol Behav 1986;38:135–138. [PubMed: 3786493]

Ferris CF, Melloni RH Jr. Koppel G, Perry KW, Fuller RW, et al. Vasopressin/serotonin interactions in the anterior hypothalamus control aggressive behavior in golden hamsters. J Neurosci 1997;17:4331–4340. [PubMed: 9151749]

Ferris CF, Potegal M. Vasopressin receptor blockade in the anterior hypothalamus suppresses aggression in hamsters. Physiol Behav 1988;44:235–239. [PubMed: 2853382]

Ferris CF, Rasmussen MF, Messenger T, Koppel G. Vasopressin-dependent flank marking in golden hamsters is suppressed by drugs used in the treatment of obsessive-compulsive disorder. BMC Neurosci 2001;2:10. [PubMed: 11545675]

Ferris CF, Singer EA, Meenan DM, Albers HE. Inhibition of vasopressin-stimulated flank marking behavior by V1-receptor antagonists. Eur J Pharmacol 1988;154:153–159. [PubMed: 2976377]

Ferris CF, Stolberg T, Delville Y. Serotonin regulation of aggressive behavior in male golden hamsters (Mesocricetus auratus). Behav Neurosci 1999;113:804–815. [PubMed: 10495088]

Fetissov SO, Hallman J, Nilsson I, Lefvert AK, Oreland L, et al. Aggressive behavior linked to corticotropin-reactive autoantibodies. Biol Psychiatry 2006;60:799–802. [PubMed: 16876133]

Fink S, Excoffier L, Heckel G. Mammalian monogamy is not controlled by a single gene. Proc Natl Acad Sci U S A 2006;103:10956–10960. [PubMed: 16832060]

Foletta VC, Brown FD, Young WS 3rd. Cloning of rat ARHGAP4/C1, a RhoGAP family member expressed in the nervous system that colocalizes with the Golgi complex and microtubules. Brain Res Mol Brain Res 2002;107:65–79. [PubMed: 12414125]

Fombonne E. Epidemiological surveys of autism and other pervasive developmental disorders: an update. J Autism Dev Disord 2003;33:365–382. [PubMed: 12959416]

Frazier CR, Trainor BC, Cravens CJ, Whitney TK, Marler CA. Paternal behavior influences development of aggression and vasopressin expression in male California mouse offspring. Horm Behav 2006;50:699–707. [PubMed: 16934808]

Fujiwara M, Ohgami Y, Inada K, Iwasaki K. Effect of active fragments of arginine-vasopressin on the disturbance of spatial cognition in rats. Behav Brain Res 1997;83:91–96. [PubMed: 9062666]

Fujiwara Y, Hiroyama M, Sanbe A, Yamauchi J, Tsujimoto G, et al. Mutual regulation of vasopressin- and oxytocin-induced glucagon secretion in V1b vasopressin receptor knockout mice. J Endocrinol 2007;192:361–369. [PubMed: 17283236]

Funabashi T, Shinohara K, Mitsushima D, Kimura F. Estrogen increases arginine-vasopressin V1a receptor mRNA in the preoptic area of young but not of middle-aged female rats. Neurosci Lett 2000;285:205–208. [PubMed: 10806322]

Gaffori OJ, De Wied D. Time-related memory effects of vasopressin analogues in rats. Pharmacol Biochem Behav 1986;25:1125–1129. [PubMed: 3809214]

Gainer H, Fields RL, House SB. Vasopressin gene expression: experimental models and strategies. Exp Neurol 2001;171:190–199. [PubMed: 11573971]

Gais S, Sommer M, Fischer S, Perras B, Born J. Post-trial administration of vasopressin in humans does not enhance memory formation (vasopressin and memory consolidation). Peptides 2002;23:581–583. [PubMed: 11836010]

Geller B, Tillman R, Badner JA, Cook EH Jr. Are the arginine vasopressin V1a receptor microsatellites related to hypersexuality in children with a prepubertal and early adolescent bipolar disorder phenotype? Bipolar Disord 2005;7:610–616. [PubMed: 16403186]

Gerkema MP, Van der Zee EA, Feitsma LE. Expression of circadian rhythmicity correlates with the number of arginine-vasopressin-immunoreactive cells in the suprachiasmatic nucleus of common voles, Microtus arvalis. Brain Res 1994;639:93–101. [PubMed: 8180844]

Gobrogge KL, Liu Y, Jia X, Wang Z. Anterior hypothalamic neural activation and neurochemical associations with aggression in pair-bonded male prairie voles. J Comp Neurol 2007;502:1109–1122. [PubMed: 17444499]

Goekoop JG, de Winter RP, de Rijk R, Zwinderman KH, Frankhuijzen-Sierevogel A, et al. Depression with above-normal plasma vasopressin: validation by relations with family history of depression and mixed anxiety and retardation. Psychiatry Res 2006;141:201–211. [PubMed: 16436301]

Gold PW, Goodwin FK, Reus VI. Vasopressin in affective illness. Lancet 1978;1:1233–1236. [PubMed: 77997]

Grant FD. Genetic models of vasopressin deficiency. Exp Physiol 2000;85:203S–209S. [PubMed: 10795924]Spec No

Griebel G, Simiand J, Serradeil-Le Gal C, Wagnon J, Pascal M, et al. Anxiolyticand antidepressant-like effects of the non-peptide vasopressin V1b receptor antagonist, SSR149415, suggest an innovative approach for the treatment of stress-related disorders. Proc Natl Acad Sci U S A 2002;99:6370–6375. [PubMed: 11959912]

Grimes JM, Ricci LA, Melloni RH Jr. Plasticity in anterior hypothalamic vasopressin correlates with aggression during anabolic-androgenic steroid withdrawal in hamsters. Behav Neurosci 2006;120:115–124. [PubMed: 16492122]

Grimmelikhuijzen CJ, Spencer AN. FMRFamide immunoreactivity in the nervous system of the medusa Polyorchis penicillatus. J Comp Neurol 1984;230:361–371. [PubMed: 6151569]

Grmec S, Mally S. Vasopressin improves outcome in out-of-hospital cardiopulmonary resuscitation of ventricular fibrillation and pulseless ventricular tachycardia: a observational cohort study. Crit Care 2006;10:R13. [PubMed: 16420660]

Groblewski TA, Nunez AA, Gold RM. Circadian rhythms in vasopressin deficient rats. Brain Res Bull 1981;6:125–130. [PubMed: 7470957]

Guillon CD, Koppel G, Brownstein MJ, Chaney MO, Ferris CF, et al. Azetidinones as vasopressin V1a antagonists. Bioorg Med Chem 2007;15:2054–2080. [PubMed: 17234419]

Gulpinar MA, Yegen BC. The physiology of learning and memory: role of peptides and stress. Curr Protein Pept Sci 2004;5:457–473. [PubMed: 15581416]

Hallbeck M, Hermanson O, Blomqvist A. Distribution of preprovasopressin mRNA in the rat central nervous system. J Comp Neurol 1999;411:181–200. [PubMed: 10404247]

Hamburger-Bar R, Eisenberg J, Belmaker RH. Animal and clinical studies of vasopressin effects on learning and memory. Isr J Med Sci 1987;23:12–18. [PubMed: 2952619]

Hamburger-Bar R, Klein A, Belmaker RH. The effect of chronic vs. acute injection of vasopressin on animal learning and memory. Peptides 1985;6:23–25. [PubMed: 3991361]

Hammock EA, Young LJ. Functional microsatellite polymorphism associated with divergent social structure in vole species. Mol Biol Evol 2004;21:1057–1063. [PubMed: 15014156]

Hammock EA, Young LJ. Microsatellite instability generates diversity in brain and sociobehavioral traits. Science 2005;308:1630–1634. [PubMed: 15947188]

Hammock EA, Young LJ. Oxytocin, vasopressin and pair bonding: implications for autism. Philos Trans R Soc Lond B Biol Sci 2006;361:2187–2198. [PubMed: 17118932]

Hara Y, Battey J, Gainer H. Structure of mouse vasopressin and oxytocin genes. Brain Res Mol Brain Res 1990;8:319–324. [PubMed: 2176709]

Harrison RJ, Connor DF, Nowak C, Nash K, Melloni RH Jr. Chronic anabolic-androgenic steroid treatment during adolescence increases anterior hypothalamic vasopressin and aggression in intact hamsters. Psychoneuroendocrinology 2000;25:317–338. [PubMed: 10725610]

Hernando F, Schoots O, Lolait SJ, Burbach JP. Immunohistochemical localization of the vasopressin V1b receptor in the rat brain and pituitary gland: anatomical support for its involvement in the central effects of vasopressin. Endocrinology 2001;142:1659–1668. [PubMed: 11250948]

Hiroyama M, Aoyagi T, Fujiwara Y, Birumachi J, Shigematsu Y, et al. Hypermetabolism of fat in V1a vasopressin receptor knockout mice. Mol Endocrinol 2007;21:247–258. [PubMed: 17021052]

Hofman MA, Swaab DF. Alterations in circadian rhythmicity of the vasopressin-producing neurons of the human suprachiasmatic nucleus (SCN) with aging. Brain Res 1994;651:134–142. [PubMed: 7922560]

Howl J, Wang X, Kirk CJ, Wheatley M. Fluorescent and biotinylated linear peptides as selective bifunctional ligands for the V1a vasopressin receptor. Eur J Biochem 1993;213:711–719. [PubMed: 8477743]

Hruby VJ, Chow MS, Smith DD. Conformational and structural considerations in oxytocin-receptor binding and biological activity. Annu Rev Pharmacol Toxicol 1990;30:501–534. [PubMed: 2160792]

Hu SB, Zhao ZS, Yhap C, Grinberg A, Huang SP, et al. Vasopressin receptor 1a-mediated negative regulation of B cell receptor signaling. J Neuroimmunol 2003;135:72–81. [PubMed: 12576226]

Hut RA, Van der Zee EA, Jansen K, Gerkema MP, Daan S. Gradual reappearance of post-hibernation circadian rhythmicity correlates with numbers of vasopressin-containing neurons in the suprachiasmatic nuclei of European ground squirrels. J Comp Physiol [B] 2002;172:59–70.

Inder WJ, Donald RA, Prickett TC, Frampton CM, Sullivan PF, et al. Arginine vasopressin is associated with hypercortisolemia and suicide attempts in depression. Biol Psychiatry 1997;42:744–747. [PubMed: 9325570]

Insel TR. Is social attachment an addictive disorder? Physiol Behav 2003;79:351–357. [PubMed: 12954430]

Insel TR, Shapiro LE. Oxytocin receptor distribution reflects social organization in monogamous and polygamous voles. Proc Natl Acad Sci USA 1992;89:5981–5985. [PubMed: 1321430]

Insel TR, Wang ZX, Ferris CF. Patterns of brain vasopressin receptor distribution associated with social organization in microtine rodents. J Neurosci 1994;14:5381–5392. [PubMed: 8083743]

Insel TR, Winslow JT, Williams JR, Hastings N, Shapiro LE, et al. The role of neurohypophyseal peptides in the central mediation of complex social processes--evidence from comparative studies. Regul Pept 1993;45:127–131. [PubMed: 8511334]

Ishunina TA, Swaab DF. Neurohypophyseal peptides in aging and Alzheimer's disease. Ageing Res Rev 2002;1:537–558. [PubMed: 12067600]

Itoh S, Yamada S, Mori T, Miwa T, Tottori K, et al. Attenuated stress-induced catecholamine release in mice lacking the vasopressin V1b receptor. Am J Physiol Endocrinol Metab 2006;291:E147–151. [PubMed: 16464910]

Izquierdo LA, Barros DM, Medina JH, Izquierdo I. Stress hormones enhance retrieval of fear conditioning acquired either one day or many months before. Behav Pharmacol 2002;13:203–213. [PubMed: 12122310]

Jansen K, Van der Zee EA, Gerkema MP. Organotypic suprachiasmatic nuclei cultures of adult voles reflect locomotor behavior: differences in number of vasopressin cells. Chronobiol Int 1999;16:745–750. [PubMed: 10584174]

Jansen K, Van der Zee EA, Gerkema MP. Being circadian or not: vasopressin release in cultured SCN mirrors behavior in adult voles. Neuroreport 2000;11:3555–3558. [PubMed: 11095517]

Jard S, Barberis C, Audigier S, Tribollet E. Neurohypophyseal hormone receptor systems in brain and periphery. Prog Brain Res 1987;72:173–187. [PubMed: 3039574]

Johnson AE, Audigier S, Rossi F, Jard S, Tribollet E, et al. Localization and characterization of vasopressin binding sites in the rat brain using an iodinated linear AVP antagonist. Brain Res 1993;622:9–16. [PubMed: 8242389]

Johnson AE, Barberis C, Albers HE. Castration reduces vasopressin receptor binding in the hamster hypothalamus. Brain Res 1995;674:153–158. [PubMed: 7773686]

Kalamatianos T, Kallo I, Coen CW. Ageing and the diurnal expression of the mRNAs for vasopressin and for the V1a and V1b vasopressin receptors in the suprachiasmatic nucleus of male rats. J Neuroendocrinol 2004;16:493–501. [PubMed: 15189323]

Kalsbeek A, Palm IF, La Fleur SE, Scheer FA, Perreau-Lenz S, et al. SCN outputs and the hypothalamic balance of life. J Biol Rhythms 2006b;21:458–469. [PubMed: 17107936]

Kalsbeek A, Perreau-Lenz S, Buijs RM. A network of (autonomic) clock outputs. Chronobiol Int 2006a; 23:521–535. [PubMed: 16753939]

Keck ME, Wigger A, Welt T, Muller MB, Gesing A, et al. Vasopressin mediates the response of the combined dexamethasone/CRH test in hyper-anxious rats: implications for pathogenesis of affective disorders. Neuropsychopharmacology 2002;26:94–105. [PubMed: 11751036]

Keverne EB, Curley JP. Vasopressin, oxytocin and social behaviour. Curr Opin Neurobiol 2004;14:777–783. [PubMed: 15582383]

Kim SJ, Young LJ, Gonen D, Veenstra-VanderWeele J, Courchesne R, et al. Transmission disequilibrium testing of arginine vasopressin receptor 1A (AVPR1A) polymorphisms in autism. Mol Psychiatry 2002;7:503–507. [PubMed: 12082568]

Kleiman DG. Monogamy in mammals. Q Rev Biol 1977;52:39–69. [PubMed: 857268]

Koob GF, Lebrun C, Bluthe RM, Dantzer R, Le Moal M. Role of neuropeptides in learning versus performance: focus on vasopressin. Brain Res Bull 1989;23:359–364. [PubMed: 2686806]

Koshimizu TA, Nasa Y, Tanoue A, Oikawa R, Kawahara Y, et al. V1a vasopressin receptors maintain normal blood pressure by regulating circulating blood volume and baroreflex sensitivity. Proc Natl Acad Sci U S A 2006;103:7807–7812. [PubMed: 16682631]

Kovacs GL, Buijs RM, Bohus B, van Wimersma Greidanus TB. Microinjection of arginine8-vasopressin antiserum into the dorsal hippocampus attenuates passive avoidance behavior in rats. Physiol Behav 1982;28:45–48. [PubMed: 7079322]

Kovacs GL, Veldhuis HD, Versteeg DH, De Wied D. Facilitation of avoidance behavior by vasopressin fragments microinjected into limbic-midbrain structures. Brain Res 1986;371:17–24. [PubMed: 3708341]

Laczi F, Gaffori O, De Kloet ER, De Wied D. Arginine-vasopressin content of hippocampus and amygdala during passive avoidance behavior in rats. Brain Res 1983;280:309–315. [PubMed: 6652491]

Landgraf R. The involvement of the vasopressin system in stress-related disorders. CNS Neurol Disord Drug Targets 2006;5:167–179. [PubMed: 16611090]

Landgraf R, Frank E, Aldag JM, Neumann ID, Sharer CA, et al. Viral vector-mediated gene transfer of the vole V1a vasopressin receptor in the rat septum: improved social discrimination and active social behaviour. Eur J Neurosci 2003;18:403–411. [PubMed: 12887422]

Landgraf R, Gerstberger R, Montkowski A, Probst JC, Wotjak CT, et al. V1 vasopressin receptor antisense oligodeoxynucleotide into septum reduces vasopressin binding, social discrimination abilities, and anxiety-related behavior in rats. J Neurosci 1995;15:4250–4258. [PubMed: 7790909]

Landgraf R, Kessler MS, Bunck M, Murgatroyd C, Spengler D, et al. Candidate genes of anxiety-related behavior in HAB/LAB rats and mice: focus on vasopressin and glyoxalase-I. Neurosci Biobehav Rev 2007;31:89–102. [PubMed: 16934871]

Landgraf R, Neumann I, Pittman QJ. Septal and hippocampal release of vasopressin and oxytocin during late pregnancy and parturition in the rat. Neuroendocrinology 1991;54:378–383. [PubMed: 1758580]

Landgraf R, Neumann I, Russell JA, Pittman QJ. Push-pull perfusion and microdialysis studies of central oxytocin and vasopressin release in freely moving rats during pregnancy, parturition, and lactation. Ann N Y Acad Sci 1992;652:326–339. [PubMed: 1626836]

Landgraf R, Wigger A, Holsboer F, Neumann ID. Hyper-reactive hypothalamo-pituitary-adrenocortical axis in rats bred for high anxiety-related behaviour. J Neuroendocrinol 1999;11:405–407. [PubMed: 10336720]

Liebsch G, Wotjak CT, Landgraf R, Engelmann M. Septal vasopressin modulates anxiety-related behaviour in rats. Neurosci Lett 1996;217:101–104. [PubMed: 8916082]

Lim MM, Hammock EA, Young LJ. The role of vasopressin in the genetic and neural regulation of monogamy. J Neuroendocrinol 2004a;16:325–332. [PubMed: 15089970]

Lim MM, Wang Z, Olazabal DE, Ren X, Terwilliger EF, et al. Enhanced partner preference in a promiscuous species by manipulating the expression of a single gene. Nature 2004b;429:754–757. [PubMed: 15201909]

Lim MM, Young LJ. Neuropeptidergic regulation of affiliative behavior and social bonding in animals. Horm Behav 2006;50:506–517. [PubMed: 16890230]

Liu RY, Zhou JN, Hoogendijk WJ, van Heerikhuize J, Kamphorst W, et al. Decreased vasopressin gene expression in the biological clock of Alzheimer disease patients with and without depression. J Neuropathol Exp Neurol 2000;59:314–322. [PubMed: 10759187]

Lolait SJ, O'Carroll AM, Mahan LC, Felder CC, Button DC, et al. Extrapituitary expression of the rat V1b vasopressin receptor gene. Proc Natl Acad Sci U S A 1995;92:6783–6787. [PubMed: 7624319]

Lolait SJ, Stewart LQ, Jessop DS, Young WS 3rd, O'Carroll AM. The hypothalamic-pituitary-adrenal axis response to stress in mice lacking functional vasopressin V1b receptors. Endocrinology 2007a; 148:849–856. [PubMed: 17122081]

Lolait SJ, Stewart LQ, Roper JA, Harrison DS, Jessop W, et al. Attenuated stress response to acute lipopolysaccharide challenge and ethanol administration in vasopressin V1b receptor knockout mice. J Neuroendocrinol 2007b;19:543–551. [PubMed: 17561882]

Lonstein JS, De Vries GJ. Sex differences in the parental behaviour of adult virgin prairie voles: independence from gonadal hormones and vasopressin. J Neuroendocrinol 1999;11:441–449. [PubMed: 10336725]

Lonstein JS, Rood BD, De Vries GJ. Unexpected effects of perinatal gonadal hormone manipulations on sexual differentiation of the extrahypothalamic argininevasopressin system in prairie voles. Endocrinology 2005;146:1559–1567. [PubMed: 15591140]

Lord C, Cook EH, Leventhal BL, Amaral DG. Autism spectrum disorders. Neuron 2000;28:355–363. [PubMed: 11144346]

Ma DQ, Cuccaro ML, Jaworski JM, Haynes CS, Stephan DA, et al. Dissecting the locus heterogeneity of autism: significant linkage to chromosome 12q14. Mol Psychiatry 2007;12:376–384. [PubMed: 17179998]

Manning, M.; Sawyer, WH. Antagonists of vasopressin and oxytocin: current status and future perspective. In: Jard, S.; Jamison, R., editors. Vasopressin. John Libbey Eurotext Ltd; France: 1991. p. 297-309.

Manning M, Sawyer WH. Design, synthesis and some uses of receptor-specific agonists and antagonists of vasopressin and oxytocin. J Recept Res 1993;13:195–214. [PubMed: 8383753]

Mayes CR, Watts AG, McQueen JK, Fink G, Charlton HM. Gonadal steroids influence neurophysin II distribution in the forebrain of normal and mutant mice. Neuroscience 1988;25:1013–1022. [PubMed: 3405422]

Melloni RH Jr. Connor DF, Hang PT, Harrison RJ, Ferris CF. Anabolicandrogenic steroid exposure during adolescence and aggressive behavior in golden hamsters. Physiol Behav 1997;61:359–364. [PubMed: 9089753]

Menard J, Treit D. Effects of centrally administered anxiolytic compounds in animal models of anxiety. Neurosci Biobehav Rev 1999;23:591–613. [PubMed: 10073896]

Merali Z, Kent P, Du L, Hrdina P, Palkovits M, et al. Corticotropin-releasing hormone, arginine vasopressin, gastrin-releasing peptide, and neuromedin B alterations in stress-relevant brain regions of suicides and control subjects. Biol Psychiatry 2006;59:594–602. [PubMed: 16197926]

Meynen G, Unmehopa UA, van Heerikhuize JJ, Hofman MA, Swaab DF, et al. Increased arginine vasopressin mRNA expression in the human hypothalamus in depression: A preliminary report. Biol Psychiatry 2006;60:892–895. [PubMed: 16499879]

Mezey E, Kiss JZ. Coexpression of vasopressin and oxytocin in hypothalamic supraoptic neurons of lactating rats. Endocrinology 1991;129:1814–1820. [PubMed: 1915070]

Michell RH, Kirk CJ, Billah MM. Hormonal stimulation of phosphatidylinositol breakdown with particular reference to the hepatic effects of vasopressin. Biochem Soc Trans 1979;7:861–865. [PubMed: 510730]

Miczek KA, Maxson SC, Fish EW, Faccidomo S. Aggressive behavioral phenotypes in mice. Behav Brain Res 2001;125:167–181. [PubMed: 11682108]

Miller MA, De Vries GJ, al-Shamma HA, Dorsa DM. Decline of vasopressin immunoreactivity and mRNA levels in the bed nucleus of the stria terminalis following castration. J Neurosci 1992;12:2881–2887. [PubMed: 1494938]

Miller MA, Urban JH, Dorsa DM. Steroid dependency of vasopressin neurons in the bed nucleus of the stria terminalis by in situ hybridization. Endocrinology 1989;125:2335–2340. [PubMed: 2791993]

Mishima K, Tsukikawa H, Inada K, Fujii M, Iwasaki K, et al. Ameliorative effect of vasopressin-(4-9) through vasopressin V(1A) receptor on scopolamine-induced impairments of rat spatial memory in the eight-arm radial maze. Eur J Pharmacol 2001;427:43–52. [PubMed: 11553362]

Mishima K, Tsukikawa H, Miura I, Inada K, Abe K, et al. Ameliorative effect of NC-1900, a new AVP4-9 analog, through vasopressin V1A receptor on scopolamine-induced impairments of spatial memory in the eight-arm radial maze. Neuropharmacology 2003;44:541–552. [PubMed: 12646291]

Mlynarik M, Zelena D, Bagdy G, Makara GB, Jezova D. Signs of attenuated depression-like behavior in vasopressin deficient Brattleboro rats. Horm Behav 2007;51:395–405. [PubMed: 17258216]

Mohr E, Schmitz E, Richter D. A single rat genomic DNA fragment encodes both the oxytocin and vasopressin genes separated by 11 kilobases and oriented in opposite transcriptional directions. Biochimie 1988;70:649–654. [PubMed: 2844303]

Muller RA. The study of autism as a distributed disorder. Ment Retard Dev Disabil Res Rev 2007;13:85–95. [PubMed: 17326118]

Murgatroyd C, Wigger A, Frank E, Singewald N, Bunck M, et al. Impaired repression at a vasopressin promoter polymorphism underlies overexpression of vasopressin in a rat model of trait anxiety. J Neurosci 2004;24:7762–7770. [PubMed: 15342744]

Myers BL, Badia P. Changes in circadian rhythms and sleep quality with aging: mechanisms and interventions. Neurosci Biobehav Rev 1995;19:553–571. [PubMed: 8684716]

Nair HP, Young LJ. Vasopressin and pair-bond formation: genes to brain to behavior. Physiology (Bethesda) 2006;21:146–152. [PubMed: 16565480]

Nishimura H, Fan Z. Regulation of water movement across vertebrate renal tubules. Comp Biochem Physiol A Mol Integr Physiol 2003;136:479–498. [PubMed: 14613779]

O'Keefe JA, Crowley RS, Hrivnak P, Kim NB, Amico JA. Effect of testosterone and its metabolites upon the level of vasopressin messenger ribonucleic acid in the hypothalamus of the hyperosmotically stimulated male rat. Neuroendocrinology 1995;61:405–411. [PubMed: 7783853]

O'Keefe J, Dostrovsky J. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res 1971;34:171–175. [PubMed: 5124915]

Oliver G, Schafer EA. On the Physiological Action of Extracts of Pituitary Body and certain other Glandular Organs: Preliminary Communication. J Physiol 1895;18:277–279.

Oshikawa S, Tanoue A, Koshimizu TA, Kitagawa Y, Tsujimoto G. Vasopressin stimulates insulin release from islet cells through V1b receptors: a combined pharmacological/knockout approach. Mol Pharmacol 2004;65:623–629. [PubMed: 14978240]

Ostrowski NL, Lolait SJ, Bradley DJ, O'Carroll AM, Brownstein MJ, et al. Distribution of V1a and V2 vasopressin receptor messenger ribonucleic acids in rat liver, kidney, pituitary and brain. Endocrinology 1992;131:533–535. [PubMed: 1535312]

Ostrowski NL, Lolait SJ, Young WS 3rd. Cellular localization of vasopressin V1a receptor messenger ribonucleic acid in adult male rat brain, pineal, and brain vasculature. Endocrinology 1994;135:1511–1528. [PubMed: 7925112]

Paban V, Soumireu-Mourat B, Alescio-Lautier B. Behavioral effects of arginine8-vasopressin in the Hebb-Williams maze. Behav Brain Res 2003;141:1–9. [PubMed: 12672553]

Packard MG, Ettenberg A. Effects of peripherally injected vasopressin and desglycinamide vasopressin on the extinction of a spatial learning task in rats. Regul Pept 1985;11:51–63. [PubMed: 4011956]

Parker KJ, Lee TM. Central vasopressin administration regulates the onset of facultative paternal behavior in microtus pennsylvanicus (meadow voles). Horm Behav 2001;39:285–294. [PubMed: 11374914]

Pena A, Murat B, Trueba M, Ventura MA, Wo NC, et al. Design and synthesis of the first selective agonists for the rat vasopressin V(1b) receptor: based on modifications of deamino-[Cys1]arginine vasopressin at positions 4 and 8. J Med Chem 2007a;50:835–847. [PubMed: 17300166]

Pena A, Murat B, Trueba M, Ventura MA, Bertrand G, et al. Pharmacological and physiological characterization of d[Leu4, Lys8]Vasopressin, the first V1b selective agonist for rat vasopressin/oxytocin receptors. Endocrinology. 2007be pub

Perras B, Droste C, Born J, Fehm HL, Pietrowsky R. Verbal memory after three months of intranasal vasopressin in healthy old humans. Psychoneuroendocrinology 1997;22:387–396. [PubMed: 9364618]

Perreau-Lenz S, Pevet P, Buijs RM, Kalsbeek A. The biological clock: the bodyguard of temporal homeostasis. Chronobiol Int 2004;21:1–25. [PubMed: 15129821]

Phelps SM, Young LJ. Extraordinary diversity in vasopressin (V1a) receptor distributions among wild prairie voles (Microtus ochrogaster): patterns of variation and covariation. J Comp Neurol 2003;466:564–576. [PubMed: 14566950]

Pietrowsky R, Fehm-Wolfsdorf G, Born J, Fehm HL. Effects of DGAVP on verbal memory. Peptides 1988;9:1361–1366. [PubMed: 3247253]

Planas B, Kolb PE, Raskind MA, Miller MA. Vasopressin and galanin mRNAs coexist in the nucleus of the horizontal diagonal band: a novel site of vasopressin gene expression. J Comp Neurol 1995;361:48–56. [PubMed: 8550881]

Porsolt RD, Bertin A, Jalfre M. Behavioral despair in mice: a primary screening test for antidepressants. Arch Int Pharmacodyn Ther 1977;229:327–336. [PubMed: 596982]

Reppert SM, Schwartz WJ, Artman HG, Fisher DA. Comparison of the temporal profiles of vasopressin and oxytocin in the cerebrospinal fluid of the cat, monkey and rat. Brain Res 1983;261:341–345. [PubMed: 6831217]

Robinson AG. DDAVP in the treatment of central diabetes insipidus. N Engl J Med 1976;294:507–511. [PubMed: 1250255]

Roche KE, Leshner AI. ACTH and vasopressin treatments immediately after a defeat increase future submissiveness in male mice. Science 1979;204:1343–1344. [PubMed: 221973]

Saito M, Sugimoto T, Tahara A, Kawashima H. Molecular cloning and characterization of rat V1b vasopressin receptor: evidence for its expression in extra-pituitary tissues. Biochem Biophys Res Commun 1995;212:751–757. [PubMed: 7626108]

Saito M, Tahara A, Sugimoto T. 1-desamino-8-D-arginine vasopressin (DDAVP) as an agonist on V1b vasopressin receptor. Biochem Pharmacol 1997;53:1711–1717. [PubMed: 9264324]

Saito T, Ishikawa S, Abe K, Kamoi K, Yamada K, et al. Acute aquaresis by the nonpeptide arginine vasopressin (AVP) antagonist OPC-31260 improves hyponatremia in patients with syndrome of inappropriate secretion of antidiuretic hormone (SIADH). J Clin Endocrinol Metab 1997;82:1054–1057. [PubMed: 9100572]

Salome N, Stemmelin J, Cohen C, Griebel G. Differential roles of amygdaloid nuclei in the anxiolytic- and antidepressant-like effects of the V1b receptor antagonist, SSR149415, in rats. Psychopharmacology (Berl) 2006;187:237–244. [PubMed: 16779555]

Sato T, Ishida T, Irifune M, Tanaka K, Hirate K, et al. Effect of NC-1900, an active fragment analog of arginine vasopressin, and inhibitors of arachidonic acid metabolism on performance of a passive avoidance task in mice. Eur J Pharmacol 2007;560:36–41. [PubMed: 17303115]

Sebat J, Lakshmi B, Malhotra D, Troge J, Lese-Martin C, et al. Strong association of de novo copy number mutations with autism. Science 2007;316:445–449. [PubMed: 17363630]

Serradeil-Le Gal C, Derick S, Brossard G, Manning M, Simiand J, et al. Functional and pharmacological characterization of the first specific agonist and antagonist for the V1b receptor in mammals. Stress 2003;6:199–206. [PubMed: 13129813]

Serradeil-Le Gal C, Wagnon J, Simiand J, Griebel G, Lacour C, et al. Characterization of (2S,4R)-1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxy-phenyl) -2-oxo-2,3-dihydro-1H-indol-3-yl]-4-hydroxy-N,N-dimethyl-2-pyrrolidine carboxamide (SSR149415), a selective and orally active vasopressin V1b receptor antagonist. J Pharmacol Exp Ther 2002b;300:1122–1130. [PubMed: 11861823]

Serradeil-Le Gal C, Wagnon J, Tonnerre B, Roux R, Garcia G, et al. An overview of SSR149415, a selective nonpeptide vasopressin V(1b) receptor antagonist for the treatment of stress-related disorders. CNS Drug Rev 2005;11:53–68. [PubMed: 15867952]

Serradeil-Le Gal C, Wagnon J, Valette G, Garcia G, Pascal M, et al. Nonpeptide vasopressin receptor antagonists: development of selective and orally active V1a, V2 and V1b receptor ligands. Prog Brain Res 2002;139:197–210. [PubMed: 12436936]

Serradeil-Le Gal C, Wagnon J, Valette G, Garcia G, Pascal M, et al. Nonpeptide vasopressin receptor antagonists: development of selective and orally active V1a, V2 and V1b receptor ligands. Prog Brain Res 2002a;139:197–210. [PubMed: 12436936]

Shapiro RA, Xu C, Dorsa DM. Differential transcriptional regulation of rat vasopressin gene expression by estrogen receptor alpha and beta. Endocrinology 2000;141:4056–4064. [PubMed: 11089536]

Sheline YI, Gado MH, Price JL. Amygdala core nuclei volumes are decreased in recurrent major depression. Neuroreport 1998;9:2023–2028. [PubMed: 9674587]

Shimazaki T, Iijima M, Chaki S. The pituitary mediates the anxiolytic-like effects of the vasopressin V1B receptor antagonist, SSR149415, in a social interaction test in rats. Eur J Pharmacol 2006;543:63–67. [PubMed: 16843459]

Siegel, HI. Aggressive Behavior. In: Siegel, HI., editor. The Hamster: Reproduction and Behavior. Plenum Press; New York: 1985. p. 261-286.

Stemmelin J, Lukovic L, Salome N, Griebel G. Evidence that the lateral septum is involved in the antidepressant-like effects of the vasopressin V1b receptor antagonist, SSR149415. Neuropsychopharmacology 2005;30:35–42. [PubMed: 15367924]

Stribley JM, Carter CS. Developmental exposure to vasopressin increases aggression in adult prairie voles. Proc Natl Acad Sci U S A 1999;96:12601–12604. [PubMed: 10535968]

Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000;157:1552–1562. [PubMed: 11007705]

Szot P, Bale TL, Dorsa DM. Distribution of messenger RNA for the vasopressin V1a receptor in the CNS of male and female rats. Brain Res Mol Brain Res 1994;24:1–10. [PubMed: 7968346]

Taga C, Sugimoto Y, Nishiga M, Fujii Y, Kamei C. Effects of vasopressin on histamine H(1) receptor antagonist-induced spatial memory deficits in rats. Eur J Pharmacol 2001;423:167–170. [PubMed: 11448481]

Tanoue A, Ito S, Honda K, Oshikawa S, Kitagawa Y, et al. The vasopressin V1b receptor critically regulates hypothalamic-pituitary-adrenal axis activity under both stress and resting conditions. J Clin Invest 2004;113:302–309. [PubMed: 14722621]

Tecott LH. The genes and brains of mice and men. Am J Psychiatry 2003;160:646–656. [PubMed: 12668350]

Thibonnier M, Coles P, Thibonnier A, Shoham M. Molecular pharmacology and modeling of vasopressin receptors. Prog Brain Res 2002;139:179–96. [PubMed: 12436935]

Thompson R, Gupta S, Miller K, Mills S, Orr S. The effects of vasopressin on human facial responses related to social communication. Psychoneuroendocrinology 2004;29:35–48. [PubMed: 14575728]

Thompson RR, George K, Walton JC, Orr SP, Benson J. Sex-specific influences of vasopressin on human social communication. Proc Natl Acad Sci U S A 2006;103:7889–7894. [PubMed: 16682649]

Tribollet E, Barberis C, Arsenijevic Y. Distribution of vasopressin and oxytocin receptors in the rat spinal cord: sex-related differences and effect of castration in pudendal motor nuclei. Neuroscience 1997;78:499–509. [PubMed: 9145805]

Tuppy H. The amino-acid sequence in oxytocin. Biochim Biophys Acta 1953;11:449–450. [PubMed: 13093758]

Turner RA, Pierce JG, Du Vigneaud V. The purification and the animo acid content of vasopressin preparations. J Biol Chem 1951;191:21–28. [PubMed: 14850440]

Vaccari C, Lolait SJ, Ostrowski NL. Comparative distribution of vasopressin V1b and oxytocin receptor messenger ribonucleic acids in brain. Endocrinology 1998;139:5015–5033. [PubMed: 9832441]

Van der Veen DR, Castillo MR, Van der Zee EA, Jansen K, Gerkema MP, et al. Circadian dynamics of vasopressin in mouse selection lines: translation and release in the SCN. Brain Res 2005;1060:16–25. [PubMed: 16198320]

Van der Zee EA, Jansen K, Gerkema MP. Severe loss of vasopressin-immunoreactive cells in the suprachiasmatic nucleus of aging voles coincides with reduced circadian organization of running wheel activity. Brain Res 1999;816:572–579. [PubMed: 9878882]

van Leeuwen FW, Caffe AR, De Vries GJ. Vasopressin cells in the bed nucleus of the stria terminalis of the rat: sex differences and the influence of androgens. Brain Res 1985;325:391–394. [PubMed: 3978433]

van Londen L, Goekoop JG, van Kempen GM, Frankhuijzen-Sierevogel AC, Wiegant VM, et al. Plasma levels of arginine vasopressin elevated in patients with major depression. Neuropsychopharmacology 1997;17:284–292. [PubMed: 9326754]

Van Someren EJ. Circadian rhythms and sleep in human aging. Chronobiol Int 2000;17:233–243. [PubMed: 10841205]

van West D, Del-Favero J, Aulchenko Y, Oswald P, Souery D, et al. A major SNP haplotype of the arginine vasopressin 1B receptor protects against recurrent major depression. Mol Psychiatry 2004;9:287–292. [PubMed: 15094789]

Vawter MP, De Wied D, Van Ree JM. Vasopressin fragment, AVP-(4-8), improves long-term and short-term memory in the hole board search task. Neuropeptides 1997;31:489–494. [PubMed: 9413027]

Veenema AH, Blume A, Niederle D, Buwalda B, Neumann ID. Effects of early life stress on adult male aggression and hypothalamic vasopressin and serotonin. Eur J Neurosci 2006;24:1711–1720. [PubMed: 17004935]

Virkkunen M, Rawlings R, Tokola R, Poland RE, Guidotti A, et al. CSF biochemistries, glucose metabolism, and diurnal activity rhythms in alcoholic, violent offenders, fire setters, and healthy volunteers. Arch Gen Psychiatry 1994;51:20–27. [PubMed: 7506515]

Vongraven D. Die nierenwirkung von hypophysenextrakten meschen. Berl Klin Wochenscgr 1913;50:2083–2086.

Wang Z, Bullock NA, De Vries GJ. Sexual differentiation of vasopressin projections of the bed nucleus of the stria terminals and medial amygdaloid nucleus in rats. Endocrinology 1993;132:2299–2306. [PubMed: 8504734]

Wang Z, De Vries GJ. Testosterone effects on paternal behavior and vasopressin immunoreactive projections in prairie voles (Microtus ochrogaster). Brain Res 1993;631:156–160. [PubMed: 8298988]

Wang Z, De Vries GJ. Androgen and estrogen effects on vasopressin messenger RNA expression in the medial amygdaloid nucleus in male and female rats. J Neuroendocrinol 1995;7:827–831. [PubMed: 8748118]

Wang Z, Ferris CF, De Vries GJ. Role of septal vasopressin innervation in paternal behavior in prairie voles (Microtus ochrogaster). Proc Natl Acad Sci U S A 1994;91:400–404. [PubMed: 8278401]

Wang Z, Liu Y, Young LJ, Insel TR. Hypothalamic vasopressin gene expression increases in both males and females postpartum in a biparental rodent. J Neuroendocrinol 2000;12:111–120. [PubMed: 10718906]

Wang Z, Toloczko D, Young LJ, Moody K, Newman JD, et al. Vasopressin in the forebrain of common marmosets (Callithrix jacchus): studies with in situ hybridization, immunocytochemistry and receptor autoradiography. Brain Res 1997;768:147–156. [PubMed: 9369311]

Wang ZX, Liu Y, Young LJ, Insel TR. Hypothalamic vasopressin gene expression increases in both males and females postpartum in a biparental rodent. J Neuroendocrinol 2000;12:111–120. [PubMed: 10718906]

Wang Z, Young LJ, De Vries GJ, Insel TR. Voles and vasopressin: a review of molecular, cellular, and behavioral studies of pair bonding and paternal behaviors. Prog Brain Res 1998;119:483–499. [PubMed: 10074808]

Wassink TH, Piven J, Vieland VJ, Pietila J, Goedken RJ, et al. Examination of AVPR1a as an autism susceptibility gene. Mol Psychiatry 2004;9:968–972. [PubMed: 15098001]

Wenzel V, Krismer AC, Arntz HR, Sitter H, Stadlbauer KH, et al. A comparison of vasopressin and epinephrine for out-of-hospital cardiopulmonary resuscitation. N Engl J Med 2004;350:105–113. [PubMed: 14711909]

Wersinger SR, Caldwell HK, Christiansen M, Young WS 3rd. Disruption of the vasopressin 1b receptor gene impairs the attack component of aggressive behavior in mice. Genes Brain Behav 2007a; 6:653–660. [PubMed: 17284170]

Wersinger SR, Caldwell HK, Martinez L, Gold P, Hu SB, et al. Vasopressin 1a receptor knockout mice have a subtle olfactory deficit but normal aggression. Genes Brain Behav 2007b;6:540–551. [PubMed: 17083331]

Wersinger SR, Temple JL, Caldwell HK, Young WS 3rd. Inactivation of the oxytocin and the vasopressin 1b receptor genes, but not the vasopressin 1a receptor gene, differentially impair the Bruce effect in laboratory mice (*Mus musculus*). Endocrinology. 2007cEpub Oct 18

Wersinger SR, Ginns EI, O'Carroll AM, Lolait SJ, Young WS 3rd. Vasopressin V1b receptor knockout reduces aggressive behavior in male mice. Mol Psychiatry 2002;7:975–984. [PubMed: 12399951]

Wersinger SR, Kelliher KR, Zufall F, Lolait SJ, O'Carroll AM, et al. Social motivation is reduced in vasopressin 1b receptor null mice despite normal performance in an olfactory discrimination task. Horm Behav 2004;46:638–645. [PubMed: 15555506]

West CH, Weiss JM. A selective test for antidepressant treatments using rats bred for stress-induced reduction of motor activity in the swim test. Psychopharmacology (Berl) 2005;182:9–23. [PubMed: 16047194]

Wigger A, Sanchez MM, Mathys KC, Ebner K, Frank E, et al. Alterations in central neuropeptide expression, release, and receptor binding in rats bred for high anxiety: critical role of vasopressin. Neuropsychopharmacology 2004;29:1–14. [PubMed: 12942143]

Williams JR, Insel TR, Harbaugh CR, Carter CS. Oxytocin administered centrally facilitates formation of a partner preference in female prairie voles (Microtus ochrogaster). J Neuroendocrinol 1994;6:247–250. [PubMed: 7920590]

Winslow JT, Camacho F. Cholinergic modulation of a decrement in social investigation following repeated contacts between mice. Psychopharmacology (Berl) 1995;121:164–172. [PubMed: 8545521]

Winslow JT, Hastings N, Carter CS, Harbaugh CR, Insel TR. A role for central vasopressin in pair bonding in monogamous prairie voles. Nature 1993;365:545–548. [PubMed: 8413608]

Wong F, Blei AT, Blendis LM, Thuluvath PJ. A vasopressin receptor antagonist (VPA-985) improves serum sodium concentration in patients with hyponatremia: a multicenter, randomized, placebo-controlled trial. Hepatology 2003;37:182–191. [PubMed: 12500203]

Wotjak CT, Ganster J, Kohl G, Holsboer F, Landgraf R, et al. Dissociated central and peripheral release of vasopressin, but not oxytocin, in response to repeated swim stress: new insights into the secretory capacities of peptidergic neurons. Neuroscience 1998;85:1209–1222. [PubMed: 9681958]

Wotjak CT, Kubota M, Liebsch G, Montkowski A, Holsboer F, et al. Release of vasopressin within the rat paraventricular nucleus in response to emotional stress: a novel mechanism of regulating adrenocorticotropic hormone secretion? J Neurosci 1996;16:7725–7732. [PubMed: 8922428]

Yang MS, Gill M. A review of gene linkage, association and expression studies in autism and an assessment of convergent evidence. Int J Dev Neurosci 2007;25:69–85. [PubMed: 17236739]

Yirmiya N, Rosenberg C, Levi S, Salomon S, Shulman C, et al. Association between the arginine vasopressin 1a receptor (AVPR1a) gene and autism in a family-based study: mediation by socialization skills. Mol Psychiatry 2006;11:488–494. [PubMed: 16520824]

Young LJ, Hammock EA. On switches and knobs, microsatellites and monogamy. Trends Genet. 2007Epub Mar 6

Young LJ, Murphy Young AZ, Hammock EA. Anatomy and neurochemistry of the pair bond. J Comp Neurol 2005;493:51–57. [PubMed: 16255009]

Young LJ, Nilsen R, Waymire KG, MacGregor GR, Insel TR. Increased affiliative response to vasopressin in mice expressing the V1a receptor from a monogamous vole. Nature 1999;400:766–768. [PubMed: 10466725]

Young LJ, Wang Z. The neurobiology of pair bonding. Nat Neurosci 2004;7:1048–1054. [PubMed: 15452576]

Young LJ, Wang Z, Cooper TT, Albers HE. Vasopressin (V1a) receptor binding, mRNA expression and transcriptional regulation by androgen in the Syrian hamster brain. J Neuroendocrinol 2000;12:1179–1185. [PubMed: 11106975]

Young WS 3rd, Gainer H. Transgenesis and the study of expression, cellular targeting and function of oxytocin, vasopressin and their receptors. Neuroendocrinology 2003;78:185–203. [PubMed: 14583651]

Young WS 3rd, Kovacs K, Lolait SJ. The diurnal rhythm in vasopressin V1a receptor expression in the suprachiasmatic nucleus is not dependent on vasopressin. Endocrinology 1993;133:585–590. [PubMed: 8344200]

Young WS 3rd, Li J, Wersinger SR, Palkovits M. The vasopressin 1b receptor is prominent in the hippocampal area CA2 where it is unaffected by restraint stress or adrenalectomy. Neuroscience 2006;143:1031–1039. [PubMed: 17027167]

Yun J, Schoneberg T, Liu J, Schulz A, Ecelbarger CA, et al. Generation and phenotype of mice harboring a nonsense mutation in the V2 vasopressin receptor gene. J Clin Invest 2000;106:1361–1371. [PubMed: 11104789]

Zhou JN, Riemersma RF, Unmehopa UA, Hoogendijk WJ, van Heerikhuize JJ, et al. Alterations in arginine vasopressin neurons in the suprachiasmatic nucleus in depression. Arch Gen Psychiatry 2001;58:655–662. [PubMed: 11448372]

Zhou L, Blaustein JD, De Vries GJ. Distribution of androgen receptor immunoreactivity in vasopressin- and oxytocin-immunoreactive neurons in the male rat brain. Endocrinology 1994;134:2622–2627. [PubMed: 8194487]

Ziegler TE. Hormones associated with non-maternal infant care: a review of mammalian and avian studies. Folia Primatol (Basel) 2000;71:6–21. [PubMed: 10686483]

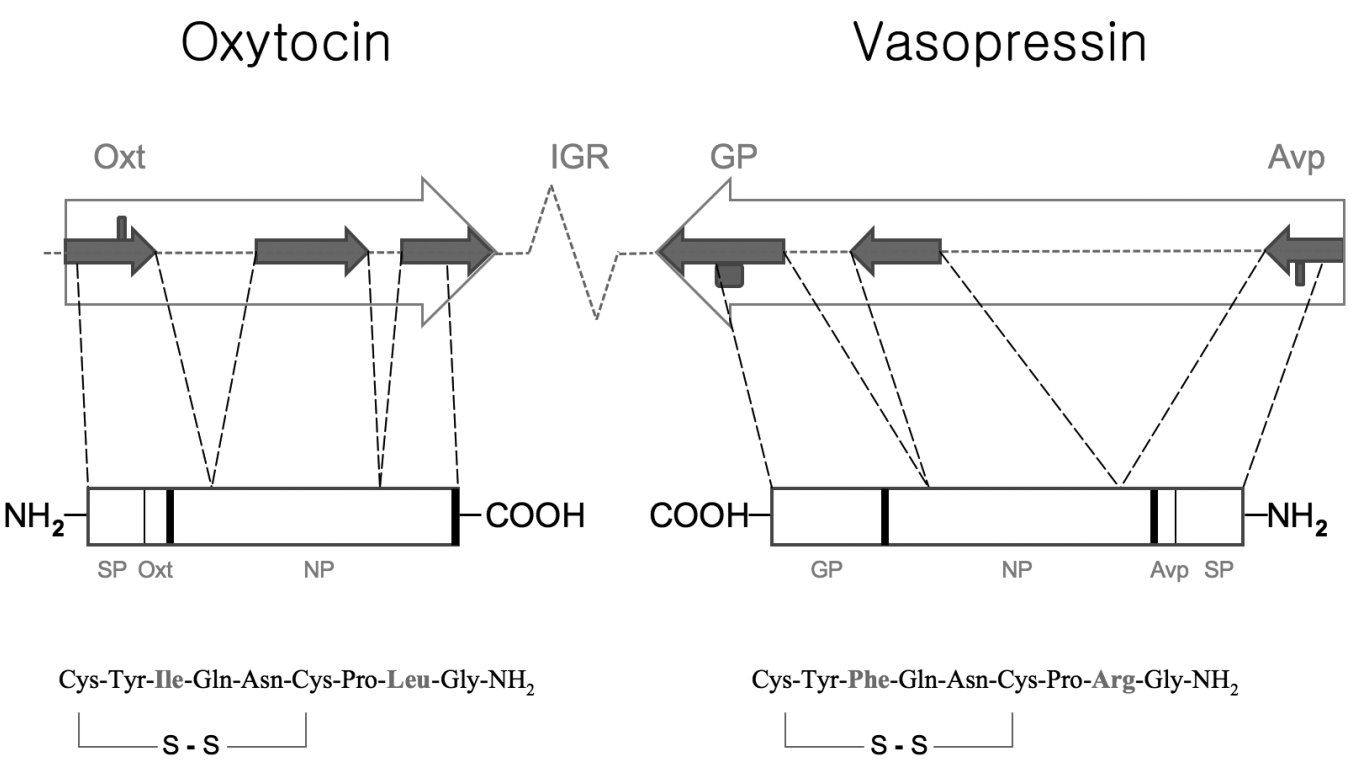

Figure 1.

Schematic diagram of the oxytocin and vasopressin genes (top, large arrows) preprohormones (middle boxes) and peptides (bottom). Both genes are composed of three exons (shown as small solid arrows) separated by two introns. The genes are located on the same chromosome but are transcribed in opposite directions and separated by an intergenic region (IGR). The IGR length varies across species. The preprohormones contain a signal peptide (SP), Avp or Oxt, neurophysin (NP), and a glycopeptide (GP) in the case of Avp. Protein processing signals are represented with thick lines. Cysteine residues form a disulfide bond to create a cyclic six amino acid ring in both peptides. Seven out of nine amino acids are common and two amino acids (bold) are different between Avp and Oxt.

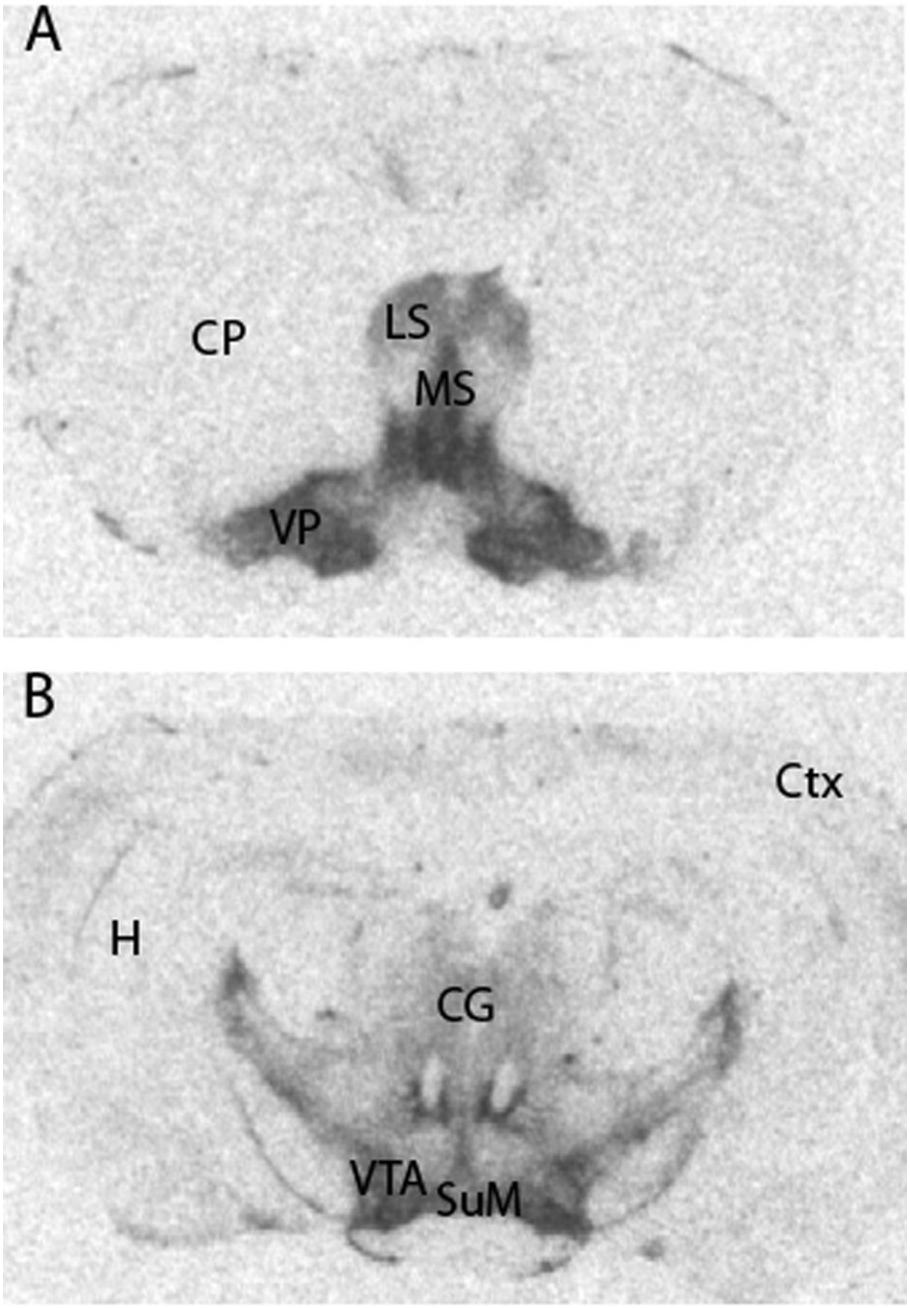

Figure 2.
Distinct distributions of Avpr1a at two levels within the mouse brain. Receptor autoradiography was performed as described (Young et al., 2000) using an ^{125}I-labeled ligand. Abbreviations: CG, central grey; CP, caudate-putamen; Ctx, neocortex; H, hippocampal formation; LS, lateral septum; MS, medial septum; Sum, supramammillary nuclei; VP, ventral pallidum; VTA, ventral tegmental area.

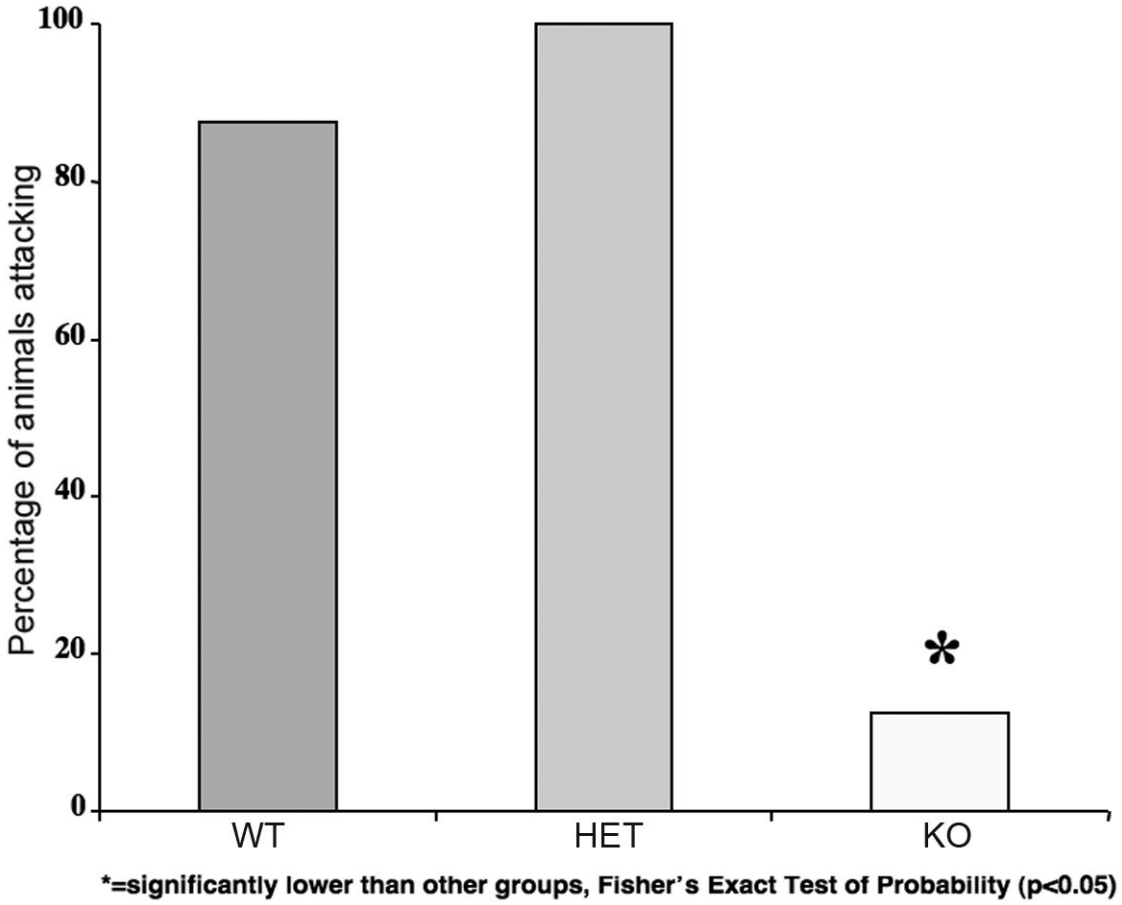

Figure 3.
Maternal aggression is much lower in Avpr1b KO mice compared to heterozygous (HET) and wildtype mice. *, $p<0.05$. Adapted from Wersinger et al. (2007a).

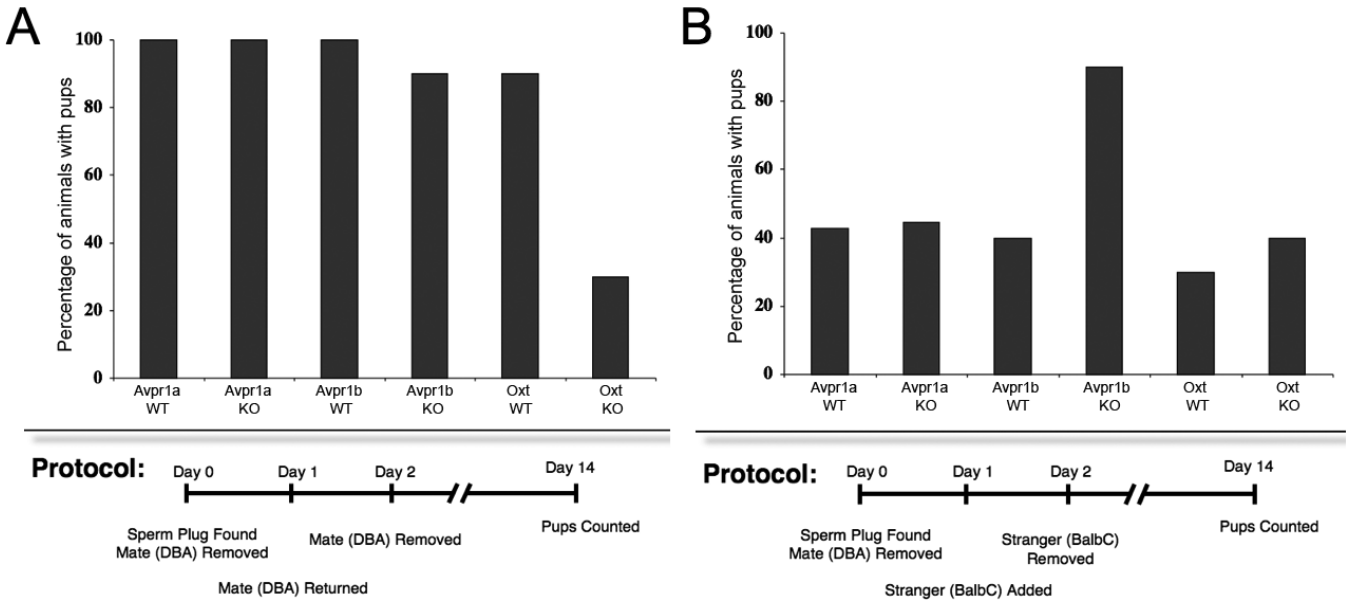

Figure 4.

Pregnancy block (Bruce effect) is normal in Avpr1a KO mice but abnormal in different ways in Avpr1b and Oxt KO mice. As expected from the severe deficit in social recognition, Oxt KO females cannot remember their mates (A) and hence do not remain pregnant. In contrast, Avpr1b KO mice do not distinguish between their mates (A) and strange males (B) and "accept" either (B). Adapted from Wersinger et al. (2007c).

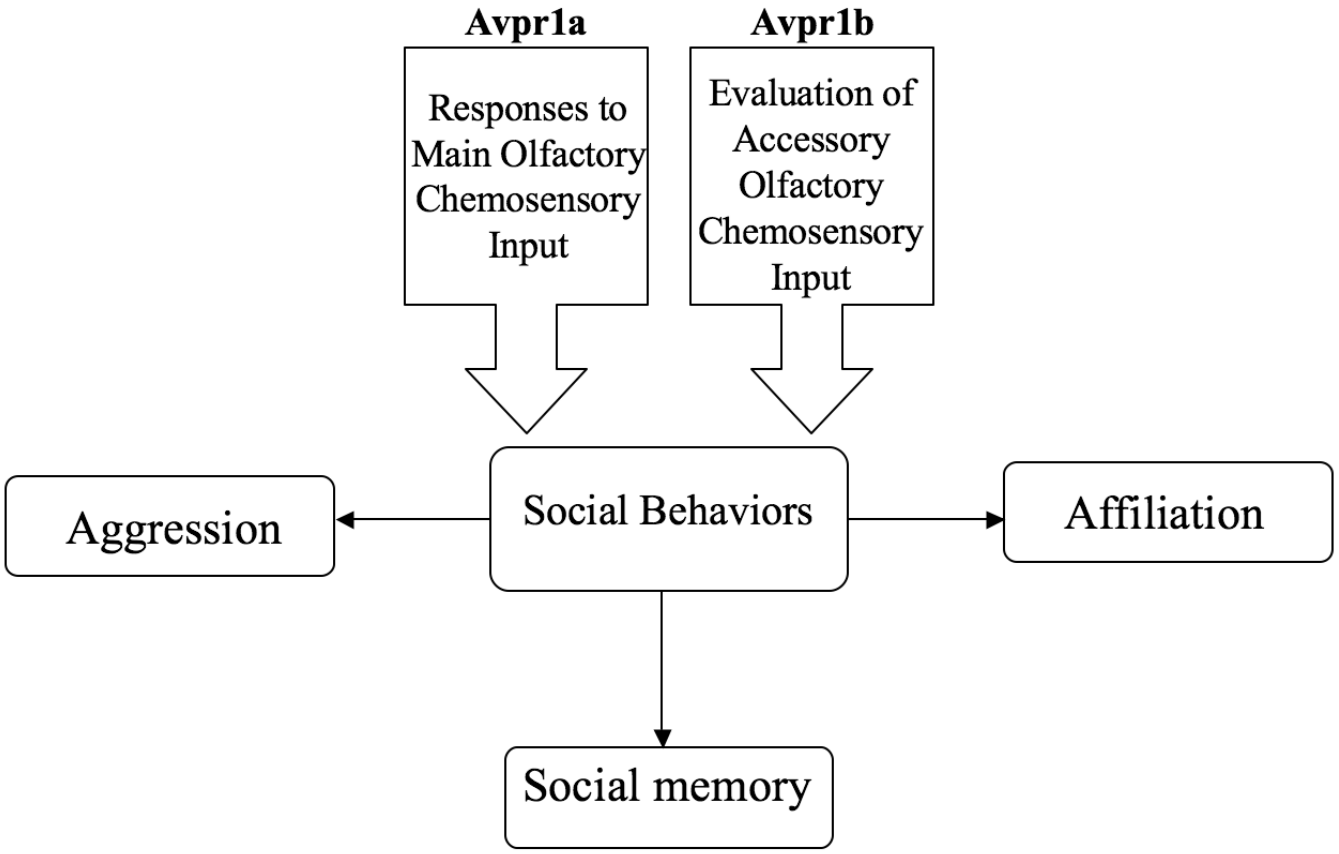

Figure 5.
Hypothesized roles of the vasopressin 1a receptor (Avpr1a) and the vasopressin 1b receptor (Avpr1b) in the regulation of social behavior. Absence of the Avpr1a results in impaired olfaction, suggestive that the Avpr1a may be important to responses to chemosensory input (Wersinger et al., 2007b). On the other hand, absence of the Avpr1b results in reduced aggression and impaired social memory in the absence of olfactory deficits (Wersinger et al., 2004; Wersinger et al., 2007a). As the Avpr1b is found predominantly within the CA2 pyramidal neurons of the hippocampus, it has been proposed to be involved in the evaluation of accessory olfactory chemosensory cues (i.e., associating the cue with the behavioral context) (Young et al., 2006).

Table 1

Pharmacological specificity of some Avp agonists and antagonists used in behavioral and physiological studies of rats.

Agent:	Avpr1a	Avpr1b	Avpr2	Oxtr
Avp	s, 1.5 ([1])	s, 0.3 ([1])	s, 0.5 ([1])	s, 1.2 ([1])
Oxt	s, 78 ([2])	s, 250 ([2])	s, 370 ([2])	s, 1.5 ([2])
[1-deamino, 8-D]Avp (DDAVP)	s, 100 ([1])	s, 9.3 ([3])	s, 0.3 ([1])	
[d(CH_2)$_5^1$,Tyr(Me)^2]Avp (Manning compound)	i, 0.3 ([2])	313 ([4])	s, 65.4 ([5])	i, 20 ([6])
SRX251	i, 0.66 ([7])			
D[Leu^4,Lys^8]Vp	3800 ([8])	s, 0.16 ([8])	100 ([8])	64 ([8])
SSR149415	1050 ([9])	i, 2.5 ([9])	2900 ([9])	270 ([9])

Approximate nM values for K_D (Oxt values) or K_i at the specific rat receptor (s=agonist, i=antagonist where known) except for SRX251 (human)

References:

[1] Pena et al., 2007a

[2] Manning and Sawyer, 1993

[3] Saito et al., 1997

[4] Antoni, 1984

[5] Howl et al., 1993

[6] Antoni and Chadio, 1989

[7] Guillon et al., 2007

[8] Pena et al., 2007b

[9] Serradeil-Le Gal et al., 2002b

Table 2

Summary of the behavioral effects of Avp

Behavioral Classes	Behaviors	Effects of Avp in rodents	Effects of Avp in humans
Social Behaviors			
Aggression	Female aggression	Maternal aggression impaired in Avpr1b knockout mice	no known effect
	Male aggression	--⇑ when injected into the AH and LS --impaired in Avpr1b KO mice	--⇑ Avp in CSF correlated with more aggressive personality
	Scent marking and grooming	⇑ when injected into the MPOA-AH of hamsters	N/A
Affiliation	Partner preference	⇑ with i.c.v. injection in male prairie voles; dependent on Avpr1a distribution	N/A
	Paternal behavior	⇑ with intraseptal or hypothalamic rise in Avp	no known effect
	Maternal behavior	⇑ hypothalamic Avp release during lactation to aid in osmotic balance	no known effect
Learning and Memory			
Social memory	Social recognition (males)	--⇑ when injected into LS --impaired in Avpr1b KO mice --impaired in Avpr1a KO mice; may be due to olfactory deficit	N/A
Non-social memory	Non-spatial memory	facilitated with Avp in dorsal or ventral hippocampus, depending on task	intranasal Avp enhances verbal memory in males, possibly by ⇑ arousal
	Spatial memory	--Avp enhances reference and working memory --impaired in Avpr1a KO mice	no known effect
Stress, Anxiety and Depression			
	Anxiety	--Avp both anxiolytic and anxiogenic, depending on antagonist differences --decreased anxiety in Avpr1a mice in some studies; sexually dimorphic --correlation in AVP release from PVN and ⇑ anxiety in rats	high plasma Avp correlated with high anxiety levels
	Depression	--correlation in AVP release from SON and PVN and ⇑ depressive-like behavior	high plasma and hypothalamic Avp associated with major depressive disorder