25 Oxytocin and Vasopressin: Genetics and Behavioral Implications

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Abstract: Oxytocin (OT) and vasopressin (VP) can profoundly affect animal physiology and behavior. Over the past 20 years, the genes that encode OT and VP, as well as their respective receptors, have been identified and intensively studied leading to a greater understanding of the hormones' functions. The use of transgenic animals, including knockout mice, and viral vectors have opened new vistas of research on the behavioral roles of OT and VP. In this chapter, we briefly review the history and the evolutionary origins of OT and VP, as well as their structures, regulation, and neuroanatomy. Finally, we highlight recently explored roles for OT and VP in physiology and behavior.

List of Abbreviations: ACTH, adrenocorticotropic hormone; AH, anterior hypothalamus; AP-2, activator protein-2; ATF-2, activating transcription factor-2; AVT, arginine vasotocin; BNST, bed nucleus of the stria terminalis; CeM, central amygdala; CNS, central nervous system; CRF, corticotropin releasing factor; DAG, diacylglycerol; ERE, estrogen response element; GRE, glucocorticoid response element; ICV, intracerebroventricularly; IGR, intergenic region; IP_3, 1,4,5 inositol triphosphate; LS, lateral septum; MeA, medial amygdala; MPOA, medial preoptic area; MPOA-AH, medial preoptic area-anterior hypothalamus; OT, oxytocin; OTKO, oxytocin knockout; OTR, oxytocin receptor; PIP_2, phosphatidylinositol 4,5-bisphosphate; PLC, phospholipase C; PVN, paraventricular nucleus; SCN, suprachiasmatic nucleus; SON, supraoptic nucleus; V1aR, vasopressin 1a receptor; V1aRKO, vasopressin 1a receptor knockout; V1bR, vasopressin 1b receptor; V1bRKO, vasopressin 1b receptor knockout; VACM-1, vasopressin-activated calcium-mobilizing receptor; VLH, ventrolateral hypothalamus; VMH, ventromedial hypothalamus; VP, vasopressin; VP-ir, vasopressin immunoreactivity

1 Overview

This is an exciting time in the field of oxytocin (OT) and vasopressin (VP) research. The important roles for OT and VP in the brain and in behavior are just now becoming understood. The use of modern molecular biological techniques as well as behavioral studies have implicated OT and VP in the regulation of a variety of behaviors. The use of viral vectors and transgenic animals, including knockout mice, has provided valuable insights into the complex roles these two hormones play in the regulation of behavior. This chapter will briefly review the history and the evolutionary origins of OT and VP, as well as their receptors, structures, regulation, and neuroanatomy. Finally, the chapter highlights recently explored roles for OT and VP in physiology and behavior.

2 History

The neurohypophysial hormones OT and VP were originally detected by Oliver and Schäfer in 1895 who demonstrated that extracts of the pituitary altered blood pressure (Oliver and Schäfer, 1895). In the decades that followed, other actions of posterior pituitary extracts were determined: in 1906, the uterine-contracting properties (Dale, 1906); in 1910, the milk-ejection properties (Ott and Scott, 1910); and in 1913, the antidiuretic properties (Farini, 1913; Vongraven, 1913). However, it was not until 1952 that du Vigneaud and colleagues isolated two distinct peptides to which specific activities could be ascribed (du Vigneaud, 1952). Following this finding, the amino acid sequences and structures of OT (Tuppy, 1953; du Vigneaud et al., 1953b) and VP (Turner et al., 1951; Archer and du Vigneaud, 1953; du Vigneaud et al., 1953a) were elucidated, followed shortly by their syntheses (du Vigneaud et al., 1954a, b). In 1955, du Vigneaud won the Nobel Prize in Chemistry due, in part, to his early descriptions and syntheses of OT and VP.

Since the 1950s, research examining the roles of OT and VP in the brain and periphery has intensified. The development of specific agonists and antagonists for OT and VP receptors has allowed for a better elucidation of the specific contributions to physiology and behavior that each peptide makes (Manning and Sawyer, 1991; Barberis et al., 1999; Serradeil-Le Gal et al., 2002). Pharmacological studies, as well as transgenic animal studies, have implicated OT and VP in the regulation of social behaviors across species. Enough scientific progress has been made so that we can now begin to integrate molecular biology and

behavior to gain a better understanding of OT and VP from the regulatory level of transcription to that of behavior.

3 Structure and Expression of Oxytocin and Vasopressin

3.1 Conservation Across Phyla

OT and VP are ancient neuropeptides that are members of a peptide family that is highly conserved across phyla (*Table 25-1*) and arose through the duplication of an ancestral vasotocin gene (Acher and Chauvet, 1995; Acher et al., 1995). OT and VP are nonapeptides with the same ring structure formed by a disulfide bridge (Hruby et al., 1990). Only the third and eighth amino acid residues differ between

Table 25-1
Vasopressin/oxytocin superfamily

Vertebrate vasopressin family		
Cys-Tyr-Phe-Gln-**Asn**-**Cys**-**Pro**-Arg-**Gly**-NH_2	Vasopressin (ADH)	Mammals[a]
Cys-Tyr-Phe-Gln-**Asn**-**Cys**-**Pro**-Lys-**Gly**-NH_2	Lysipressin	Pigs, hippopotamuses, warthogs, some marsupials
Cys-Phe-Phe-Gln-**Asn**-**Cys**-**Pro**-Arg-**Gly**-NH_2	Phenypressin	Some marsupials
Cys-Tyr-Ile-Gln-**Asn**-**Cys**-**Pro**-Arg-**Gly**-NH_2	Vasotocin[b]	Nonmammals
Vertebrate Oxytocin Family		
Cys-Tyr-Ile-Gln-**Asn**-**Cys**-**Pro**-Leu-**Gly**-NH_2	Oxytocin	Mammals[c], ratfish
Cys-Tyr-Ile-Gln-**Asn**-**Cys**-**Pro**-Ile-**Gly**-NH_2	Mesotocin	Marsupials, birds, reptiles, amphibians, lungfishes
Cys-Tyr-Ile-Ser-**Asn**-**Cys**-**Pro**-Ile-**Gly**-NH_2	Isotocin	Bony fishes
Cys-Tyr-Ile-N/Q-**Asn**-**Cys**-**Pro**-L/V-**Gly**-NH_2	Various tocins	Sharks
Invertebrate VP/OT Superfamily		
Cys-Leu-Ile-Thr-**Asn**-**Cys**-**Pro**-Arg-**Gly**-NH_2	Diuretic hormone	Locust
Cys-Phe-Val-Arg-**Asn**-**Cys**-**Pro**-Thr-**Gly**-NH_2	Annetocin	Earthworm
Cys-Phe-Ile-Arg-**Asn**-**Cys**-**Pro**-Lys-**Gly**-NH_2	Lys-Connopressin	Geography and imperial cones, pond snail, sea hare, leech
Cys-Ile-Ile-Arg-**Asn**-**Cys**-**Pro**-Arg-**Gly**-NH_2	Arg-Connopressin	Striped cone
Cys-Tyr-Phe-Arg-**Asn**-**Cys**-**Pro**-Ile-**Gly**-NH_2	Cephalotocin	Octopus
Cys-Phe-Trp-Thr-Ser-**Cys**-**Pro**-Ile-**Gly**-NH_2	Octopressin	Octopus

[a]Vasopressin is not found in some marsupials, pigs, and some other mammals

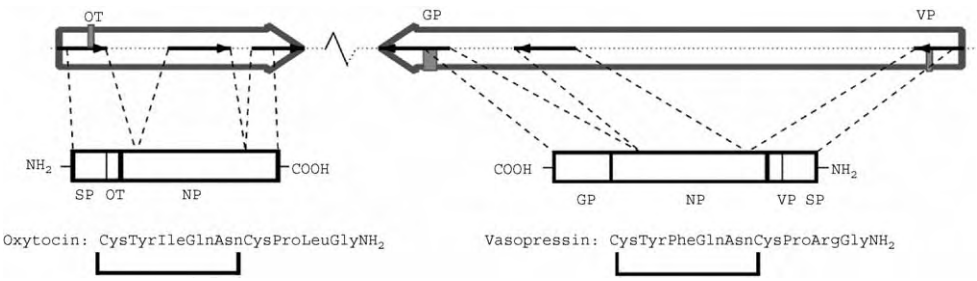
[b]Vasotocin is the progenitor of the vertebrate neurohypophysial hormones. Only vasotocin is found in hagfish and lampreys

[c]Oxytocin is also found in some marsupials (Agnatha appeared 500 million years ago)

the two peptides (◉ *Table 25-1*, ◉ *Figure 25-1*). Even in the most primitive of organisms, such as the freshwater hydra, an OT/VP-like compound is found (Grimmelikhuijzen, 1984). In general, nonmammalian tetrapods use mesotocin and vasotocin instead of the mammalian OT and VP, respectively. Bony fish have isotocin and vasotocin which correspond to the mammalian OT and VP (Acher, 1990). Exceptions to these rules are shown in ◉ *Table 25-1* (e.g., the primitive ratfish has OT and some mammals have mesotocin).

◘ Figure 25-1

Schematic representation of the oxytocin and vasopressin genes (*top*, *large arrows*), mRNAs (*middle boxes*), and the neuropeptides themselves (*bottom*). The arrows point from the 5′- to the 3′- ends of the genes. NH_2 and COOH indicate the amino and carboxy termini, respectively. Abbreviations: GP, glycopeptide; SP, signalpeptide; NP, neurophysin



3.2 Chromosomal Arrangement

The OT and VP genes are similar in structure and are oriented in opposing transcriptional directions on the same chromosome (Hara et al., 1990) (◉ *Figure 25-1*). These genes are found on chromosome 2 in mice, chromosome 3 in rats, and chromosome 20 in humans (Dutil et al., 2001) (◉ *Table 25-2*). The transcriptional units are separated by a region of DNA known as the intergenic region (IGR). The IGR shows variability across species, being 10–11 kbp in length in rat and human (Mohr et al., 1998; Gainer et al., 2001) and approximately 3.6 kbp in length in mouse (Hara et al., 1990). The IGR is particularly interesting because portions of it appear to be necessary for normal OT and VP gene expression within the hypothalamus (Fields et al., 2003; Young III and Gainer, 2003). The OT and VP genes are composed of three exons: the first exon encodes the signal peptide, the nonapeptide, and the first nine amino acid residues of the neurophysin protein; the second exon encodes the central portion of the neurophysin; and the third exon encodes the C-terminal part of the neurophysin as well as the glycopeptide of the VP preprohormone. The greatest amount of variability in sequence across species is found in exon 3 while the greatest conservation is found in exon 2 (Ivell and Richter, 1984; Ruppert et al., 1984; Sausville et al., 1985; Hara et al., 1990).

3.3 Coding and Synthesis

As noted above, both OT and VP are synthesized as part of a precursor preprohormone. Each preprohormone is cleaved resulting in the release of a nonapeptide, a neurophysin, and, in the case of VP, a glycopeptide (also known as copeptin), as it is transported along the axon (Brownstein et al., 1980). The bulk of the processing of the preprohormones occurs in the acidic environment within large, dense core vesicles (approximately 160–200 nm in diameter), and includes proteolysis by prohormone convertases and carboxypeptidase H/E and amidation of the carboxy-terminal glycine to yield the final OT and VP nonapeptides (see Burbach et al., 2001; Acher et al., 2002; von Eggelkraut-Gottanka and

Table 25-2
Gene information about vasopressin, oxytocin, and their receptors

Gene	Species	Symbol[a]	Chromosome	Known exons	Amino acids[b]	LocusID[c]
Vasopressin	Human	AVP	20 (p13)	3	164	551
	Rat	Avp	3 (q41-q42)	3	164	24211
	Mouse	Avp	2 (73.2cM)	3	168	11998
Oxytocin	Human	OXT	20 (p13)	3	125	5020
	Rat	Oxt	3 (q36)	3	125	25504
	Mouse	Oxt	2 (73.5cM)	3	125	18429
Vasopressin 1a receptor	Human	AVPR1A	12 (q14-q15)	2	418	552
	Rat	Avpr1a	7 (q21)	2	424	25107
	Mouse	Avpr1a	10 D3 (122.1cM)	2	423	54140
Vasopressin 1b receptor	Human	AVPR1B	1 (q32)	3	424	553
	Rat	Avpr1b	13 (q13)	3	425	29462
	Mouse	Avpr1b	1 E4 (131.5cM)	3	421	26361
Vasopressin 2 receptor	Human	AVPR2	X (q28)	3	371	554
	Rat	Avpr2	X (q37)	3	371	25108
	Mouse	Avpr2	X (29.52 cM)	3	371	12000
Oxytocin receptor	Human	OXTR	3 (p25)	4	389	5021
	Rat	Oxtr	4 (q42)	4	388	25342
	Mouse	Oxtr	6 E3 (113cM)	4	388	18430
Dual AII/VP receptor[d]	Human	NALP6	11 (p15)	8	513	171389
	Rat	Nalp6	1 (q41)	7	483	171390
	Mouse	Nalp6	7 F4	7	490	101613
VACM-1 receptor[e]	Human	CUL5	11 (q22-q23)	19	780	8065
	Rat	Cul5	8 (q24)	18	780	64624
	Mouse	Cul5	9 C (53.8cM)	19	780	75717

[a]Offical gene symbol
[b]Number of amino acids in the preprohormone for vasopressin and oxytocin
[c]Available at http://www.ncbi.nlm.nih.gov/LocusLink/index.html
[d]Dual angiotensin II/vasopressin receptor
[e]Vasopressin-activated calcium-mobilizing receptor protein (VACM-1; Cullin-5)

Beck-Sickinger, 2004 and references within). While the neurophysins themselves do not seem to be biologically active, it has been suggested that they may protect either OT or VP from enzymatic damage or are important for normal packaging (de Bree, 2000) and processing (Legros and Geenen, 1996) in neurosecretory vesicles. Recently, it has been suggested that the function of the glycopeptide is to help in the folding of the VP precursor which, in the absence of the glycopeptide, is less stable than the OT counterpart (Barat et al., 2004).

By far, most OT and VP are synthesized within the magnocellular neurons of the hypothalamic supraoptic nuclei (SON) and paraventricular nuclei (PVN), and are transported along their axons to the

posterior pituitary where they are stored and ultimately released into the blood stream. Once released, VP regulates salt and water homeostasis and OT regulates parturition and lactation. Within the brain, OT and VP that are not routed to the pituitary are synthesized by and transported from smaller, parvocellular neurons located in the PVN and elsewhere. However, even the magnocellular neurons of the SON and PVN can release OT and VP from their dendrites to produce important local effects (for reviews and further references, see: Ludwig, 1998; Hirasawa et al., 2004; Landgraf and Neumann, 2004; Morris and Ludwig, 2004).

The relative numbers and the distributions of OT and VP neurons within the SON and PVN vary between species. In humans, for example, VP neurons vastly outnumber OT neurons in the SON, but are nearly equal in the PVN (see Sukhov et al., 1993 and references within). In rats, however, the numbers of these neurons are approximately equal in the two nuclei but distributed in more clearly delineated and generally separate areas (Hou-Yu et al., 1986). In an osmotically normal state, about 2–3% of magnocellular neurons contain both OT and VP, but the percentage of colocalization dramatically increases during a hyperosmolar state or lactation (Kiyama and Emson, 1990; Mezey and Kiss, 1991; Glasgow et al., 1999; Telleria-Diaz et al., 2001). The increased colocalization of VP and OT is probably to further water retention, but this is speculative. Even in those cells considered exclusively vasopressinergic or oxytocinergic, there appears to be expression of the "absent" gene at about 0.5% of the major ones (Xi et al., 1999).

There are wide distributions of OT and VP fibers within the CNS. Fibers can be found from the olfactory bulbs to the intermediate lateral column of the spinal cord (Buijs et al., 1983; De Vries et al., 1985, 1986; Buijs, 1987). In general, VP tends to be found in higher concentrations in the more rostral regions of the brain and OT in the more caudal regions (Sofroniew, 1985a; Gainer and Wray, 1994). Most of the VP and OT found in these subcortical regions are likely involved in the regulation of social and reproductive behaviors, which will be discussed later in this chapter.

3.4 Vasopressin

3.4.1 CNS Distribution

As mentioned before, the majority of VP within the CNS is expressed within the magnocellular neurons of the SON and PVN, from where it is transported to the posterior pituitary. The evidence for any extrapituitary projections from the SON is scant (Mason et al., 1984; Alonso et al., 1986). In contrast, parvocellular neurons of the PVN provide robust projections, especially to the brainstem and spinal cord. Areas innervated by VP fibers include the hippocampus and subiculum, diagonal band of Broca, locus coeruleus, solitary tract nucleus, dorsal motor nucleus of the vagus, medullary adrenergic groups, and spinal cord (Buijs, 1978; Sawchenko and Swanson, 1982; De Vries and Buijs, 1983; Millan et al., 1984).

VP is also expressed within parvocellular neurons of the suprachiasmatic nucleus (SCN), bed nucleus of the stria terminalis (BNST), and medial amygdala (MeA) (Sofroniew, 1983). Within the BNST and MeA, VP-expressing cells are sex-steroid-dependent (see below) with the males having more VP immunoreactive cells than females in some species (Caffè and Van Leeuwen, 1983; Van Leeuwen et al., 1985; De Vries et al., 1986; Buijs, 1987), but not all. For example, there appears to be no sex difference in VP-immunoreactivity (VP-ir) within the BNST and MeA of Syrian hamsters; instead, galanin may have replaced VP as the gender-dependent peptide (Miller et al., 1999). Nevertheless, there are sexual dimorphisms in brain AVT in bullfrogs and newts, suggesting that across phyla VP and VP-like compounds are sensitive to gonadal steroids (Boyd and Moore, 1992). The BNST and MeA send VP fibers to the olfactory tubercle, nucleus of the diagonal band, ventral pallidum, lateral septum, ventral hippocampus, paraventricular thalamic nuclei, zona incerta, lateral habenula, ventral tegmental area, substantia nigra, periventricular gray, median and dorsal raphe nuclei, and the locus coeruleus (De Vries et al., 1985). Neurons immunoreactive for VP have also been described within the medial and lateral septum, vertical limb of the nucleus of diagonal band of Broca, and locus coeruleus (Sofroniew, 1985b), but only those in the diagonal band have been confirmed by hybridization histochemistry (Urban et al., 1990; Planas et al., 1995; Hallbeck et al., 1999). The patterns of

VP immunostaining in four different vole species are similar to each other and to other rodents and also show similar gender dimorphisms regardless of their social behavior (see below and Wang et al., 1996). A recent hybridization histochemical study in the rat has found VP expression within several new areas, including pyramidal cells of the hippocampus, parabrachial nucleus, and a portion of the mesencephalic reticular nucleus (Hallbeck et al., 1999).

3.4.2 Regulation

In the 5′-flanking region of both the OT and VP genes, there are important regulatory elements. In most eukaryotic cells, TATA and CAAT boxes are found close to the start site of transcription and regulate basal transcription. However, the promoters for OT and VP do not contain CAAT boxes but instead have "atypical" TATA boxes (Gainer and Wray, 1994). This atypical TATA box in the VP gene (CATA) may be involved in cell-specific and physiological regulation (Ho and Murphy, 2002). As described below, OT and VP are expressed in cells in different locations within the brain (and periphery, at least for OT). How expression is specifically targeted to those areas is still largely a mystery. The majority of studies examining this issue have used transgenic animals, and certain minimal requirements for expression in some areas are being ascertained. The interested reader is referred to a recent review (Young III and Gainer, 2003). The pathways from the cell surface receptors to the *cis*-acting elements have been difficult to elucidate due to the lack of pure neuronal culture systems that express OT or VP. Nonetheless, progress is being made and a brief survey of regulatory components is presented (see Itoi et al., 2004 for a review). Many of the observations are phenomenological and await direct connection between physiological state or perturbation and VP regulation.

Perhaps the best understood regulator of VP is corticosterone. This glucocorticoid suppresses expression of VP (as well as corticotropin-releasing factor, CRF) in the parvocellular neurons of the PVN (Tramu et al., 1983; Kiss et al., 1984; Sawchenko et al., 1984; Schipper et al., 1984). A sequence resembling the consensus glucocorticoid response element (GRE) has been identified, which spans from −622 to −608 in the rat VP promoter and is proposed to act as a negative response element (Mohr and Richter, 1990). Although negative regulation by a glucocorticoid has been shown in a heterologous cell system (Iwasaki et al., 1997), a specific GRE has not been demonstrated. However, in more neuronal cell cultures, removal of sequence 5′ of −588 of the rat promoter does lead to increased reporter expression (Kim et al., 2001).

The VP gene appears to be regulated by other nuclear hormone receptors, in addition to the glucocorticoid receptor, in a region-specific manner. De Vries and colleagues noted that the density of VP fibers in the lateral septum (LS) is elevated in males compared with females and that testosterone administered to females and castrated males increases the density of VP fibers within the LS (De Vries et al., 1983). They also observed that gonadectomy in males or females reduces VP in certain regions of the brain that receive innervation from the BNST and MeA, but no reduction was observed in regions that receive innervation from the magnocellular neurons of the PVN and SON (De Vries et al., 1984, 1985). VP mRNA levels in the BNST and MeA are also testosterone dependent (Miller et al., 1989, 1992; Wang and De Vries, 1995). Their studies, as well as more recent ones by others using knockout mice, also indicate that testosterone can act through both the androgen receptor and the estrogen receptor but is a stronger regulator through the estrogen receptor (Brot et al., 1993; De Vries et al., 1994; Wang and De Vries, 1995; Plumari et al., 2002; Han and De Vries, 2003; Scordalakes and Rissman, 2004). Gonadectomy has no effect on VP-ir in Syrian hamsters (Albers et al., 1991c), but it does affect VP-ir 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 OT and VP expression (Crowley and Amico, 1993; O'Keefe et al., 1995). Androgen receptors are found in nonmagnocellular responsive neurons (Zhou et al., 1994). Estrogen receptor beta is expressed in VP magnocellular neurons (Alves et al., 1998). An estrogen response element (ERE) is found over 4kb downstream of the transcriptional start site of the rat VP gene (Shapiro et al., 2000), but whether this is the site where androgens and/or its metabolites exert their effects is unknown.

Hypovolemia or hyperosmolality are strong stimuli for the expression of VP (and OT) in magnocellular neurons of the PVN and SON, but the intracellular pathways are unclear. Hyperosmolality activates the cAMP pathway (Young III et al., 1987). Elevation of cAMP in cultured hypothalamic neurons stimulates VP expression (Sladek and Gallagher, 1993). In the absence of synaptic transmission, elevation of cAMP increases VP expression in parvocellular PVN neurons (Arima et al., 2001), and this increase can be inhibited by glucocorticoids (Kuwahara et al., 2003). It is possible that this osmotic response is mediated through two different cAMP-responsive elements (−227 to −220 and −123 to −116) (Iwasaki et al., 1997). Similarly, animals in a hyperosmotic condition have increased expression of the immediate early genes c-fos and c-jun in these nuclei (Carter and Murphy, 1990), as well as increases in the alpha isoform of activator protein-2 (AP-2) and activating transcription factor-2 (ATF-2) (Meeker and Fernandes, 2002). In the VP promoter, putative regulatory elements for cAMP and AP-2 have been identified (Mohr and Richter, 1990). Cell extracts from a nonneuronal cell line were used to show that the proximal VP promoter contains an AP-1, five E-Box, and two GC-rich transcription binding sites (Grace et al., 1999).

The SCN, site of the mammalian circadian pacemaker (see below), has also been extensively investigated. VP expression within the SCN undergoes a circadian rhythm with peak mRNA levels during the day (light-phase) in rats (Uhl and Reppert, 1986; Burbach et al., 1988; Young III et al., 1993). The SCN receives excitatory input from the retina and both excitatory and inhibitory inputs from elsewhere in the CNS, in addition to input from intrinsic neurons (Albers et al., 1991a, b; Moore, 1992). How these inputs are transduced to affect VP expression is unclear. Numerous studies have shown that regulation of immediate early genes undergo circadian rhythms (e.g., Schwartz et al., 2000), and tremendous progress has been made recently in understanding the underlying molecular biology of the circadian clock (Hastings and Herzog, 2004). For example, the E-Box element, found in many genes including VP, is recognized by transcription factors containing the basic helix–loop–helix motif and is important in the generation of rhythmic expression by BMAL1 and CLOCK proteins (Jin et al., 1999; Hastings and Herzog, 2004). Muñoz et al. defined some of the E-Box flanking sequence involved in VP circadian transcription through BMAL1 and CLOCK (Muñoz et al., 2002). Arima et al. (2002) provide evidence that the circadian rhythm of VP expression requires neural activity and a MAP kinase pathway.

Two other mechanisms appear to be involved in regulating VP expression. The first is the regulation of the poly(A) tail of the mRNA. Increases in plasma osmolality increase the length of the poly(A) tail in rats and that may serve to prolong the half-life of the VP message (Carrazana et al., 1988; Zingg et al., 1988). Interestingly, the increase in mRNA levels and the increase in mRNA poly(A) tail length induced by hyperosmolality are regulated separately. Administration of *p*-chlorophenylalanine blocks the increase in mRNA levels but does not prevent the increase in tail length (Carter and Murphy, 1989). Tail length can also be shortened by starvation (Chooi et al., 1992). The second mechanism for regulating VP expression is the distribution of the VP mRNA within the cell and its processes. Because VP mRNA is found in both axons and dendrites, sorting to different neuronal processes may be important in regulating where VP is synthesized and released, although studies examining this idea are in their infancy (Trembleau et al., 1996; Mohr and Richter, 2004). It is worth noting, as well, that many small cell lung cancers express VP, accounting for some of its pathology. These cells have been used to identify potential regulatory sites within the VP gene (North, 2000; Coulson, 2002).

3.5 Oxytocin

3.5.1 CNS Distribution

OT synthesized in the magnocellular neurons of the PVN and SON project to the posterior pituitary. Parvocellular (or, at least smaller than the magnocellular) neurons in the PVN project to similar areas in the brainstem and spinal cord as the VP neurons described previously. Parvocellular OT neurons outside the PVN have been described in mice (Castel and Morris, 1988; Jirikowski et al., 1990) and various vole species (Wang et al., 1996). However, in the rat, it appears that the PVN is responsible for most, if not all, brain OT

projections (De Vries and Buijs, 1983; Rinaman, 1998; although see Jirikowski et al., 1988). OT is not expressed in the SCN, and there are very few or no OT neurons in the BNST and MeA.

3.5.2 Regulation

Most of the work examining the promoter region of the OT gene has focused on nuclear hormone receptors and orphan receptors. Estrogen binding is observed in 10–40% of the magnocellular OT neurons of the rat PVN and SON and only occasionally in mouse OT neurons elsewhere (Jirikowski et al., 1990). OT-immunoreactive neurons are observed after short-term estradiol treatment in the rat septohippocampal nucleus, lateral subcommissural area, medial preoptic area (MPOA), perifornical regions, zona incerta, and ansa lenticularis, along with more fibers in the LS, preoptic area, striatum, and amygdala (Jirikowski et al., 1988). The human and rat promoters have proven EREs (Burbach et al., 1990; Richard and Zingg, 1990; Mohr and Schmitz, 1991), but the bovine promoter apparently does not (Adan et al., 1991). Subsequently, the most proximal ERE in the rat promoter was shown to be a composite hormone response element that responds to a variety of nuclear hormone receptors and orphan receptors (Adan et al., 1993).

There are ample studies demonstrating that in cell culture both estrogen receptor alpha and beta, thyroid hormone receptors, retinoic acid receptors, and some orphan receptors can stimulate the transcription of OT (Richard and Zingg, 1990; Adan et al., 1992; Burbach et al., 1992, 1993; Vasudevan et al., 2001). However, one study provides strong evidence that retinoic acid actually represses activity from this element (Lipkin et al., 1992), but the reason for this discrepancy is unknown. Interesting recent studies suggest that steroid hormone receptors may not, in fact, act directly upon the promoter to affect transcription, but instead influence other transacting factors, either directly or through kinases (Stedronsky et al., 2002).

In vivo studies support the idea that both OT and VP are regulated by estrogen and thyroid hormones in the hypothalamus (Burbach and Adan, 1993; Dellovade et al., 1999; Ciosek, 2002; Nomura et al., 2002; Patisaul et al., 2003); although this may not always be through direct effects within the synthesizing neurons (Sladek and Somponpun, 2004). Progesterone may also directly activate expression of OT in the PVN (Thomas et al., 1999).

As with VP, hyperosmolality increases OT mRNA levels independent of an increase in poly(A) tail length (Carter and Murphy, 1989), but this effect is dependent upon gonadal steroids, since gonadectomy blocks this increase (Crowley and Amico, 1993). Increases in OT mRNA are also accompanied by increases in c-fos protein (Giovannelli et al., 1992). Interestingly, OT transcript poly(A) tail length also increases during pregnancy and lactation (Zingg and Lefebvre, 1989).

4 Vasopressin and Oxytocin Receptors

4.1 The Vasopressin Receptors

There are two principle classes of VP receptors: V1 and V2 receptors (V1R and V2R, respectively), both of which are seven transmembrane G-protein-coupled receptors. Activation of the V2R increases cAMP that mediates the classical antidiuretic effects of vasopressin. The V1Rs are coupled to $G_{\alpha q/11}$ GTP binding proteins, which along with $G_{\beta\lambda}$, activate phopholipase C (PLC) activity (Michell et al., 1979; Jard et al., 1987). PLC then generates 1,4,5-inositol triphosphate (IP_3) and diacylglycerol (DAG) from phosphatidylinositol 4,5-bisphosphate (PIP_2). IP_3 facilitates the release of intracellular Ca^{2+} stores while DAG activates protein kinase C to modulate cellular activity. There are two subtypes of the V1R: V1aR and V1bR. In the periphery, V1aR mediates the effects of VP on vasoconstriction and can be found in liver, kidney, platelets, and smooth muscle (Ostrowski et al., 1992; Watters et al., 1998). Centrally, V1aR is found in a variety of brain nuclei (Ostrowski et al., 1992, 1994; Szot et al., 1994), where it has been implicated in the regulation of several social behaviors, including social recognition, affiliative behavior, aggressive behavior, and scent marking behavior (Ferris et al., 1984, 1997; Albers and Ferris, 1985; Albers et al., 1986; Winslow et al., 1993).

The V1bR (sometimes called V3R) was originally described in the pituitary (Antoni, 1984; Jard et al., 1986; Arsenijevic et al., 1994) and finally cloned (Lolait et al., 1995). Subsequently, V1bR was also found in the brain as well as in several peripheral tissues (Arsenijevic et al., 1994; Lolait et al., 1995). More recently, V1bR has been linked to stress adaptation (Volpi et al., 2004a) and aggressive behavior in mice (Wersinger et al., 2002). There is no conclusive evidence for expression of the V2R within the CNS. Transcription of the ARHGAP4 gene within the CNS overlaps the transcription of V2R, and reverse transcriptase-PCR analysis must must be carried out under specific conditions to avoid this "contaminant" (Foletta et al., 2002). Readers interested in the actions of VP at the renal V2R and V1aR are referred to some excellent reviews (Bankir, 2001; Inoue et al., 2001).

Recent work has indicated that there are other proteins in the brain that bind VP (❯ *Table 25-2*). The vasopressin-activated calcium-mobilizing receptor protein (i.e. VACM-1or Cullin-5) and the dual angiotensin II/vasopressin receptors have widespread neuronal distributions (Hurbin et al., 2000; Ceremuga et al., 2003a). The former receptor is coupled to the phosphoinositol pathway (Burnatowska-Hledin et al., 1995) and the latter to the adenylate cyclase system (Ruiz-Opazo et al., 1995). The roles, of these receptors in the brain, including behavioral roles, are unknown, however, levels of Cullin-5 increase in the cerebral cortex and, to a lesser extent, in the hypothalamus following water deprivation (Ceremuga et al., 2003b). (❯ *Table 25-2*) summarizes genetic information about VP, OT, and their receptors.

4.1.1 CNS Distribution

The distribution of V1aR expression within the 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. The former technique was greatly facilitated through the use of specific and potent ^{125}I-labeled V1aR antagonists (Johnson et al., 1993; Kremarik et al., 1993). Prominent V1aR binding is present in the rat 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). V1aR binding is moderate throughout the spinal cord, but with higher binding 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 V1aR transcripts are found extensively throughout the rat CNS, being especially prominent, for example, 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 VP (and OT) 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, and these differences will be mentioned below when correlations are possible.

The V1bR was originally described in the anterior pituitary where it facilitates the release of adrenocorticotropic hormone (ACTH) from the corticotropes (Jard et al., 1987; Antoni, 1993). V1bR in the pituitary helps mediate the effects of VP on the hypothalamic–pituitary–adrenal axis, which is the regulator of the stress response in mammals (Volpi et al., 2004a). V1bR mRNA is also found in a variety of peripheral tissues including kidney, thymus, heart, lung, spleen, uterus, and breast (Lolait et al., 1995), although its role in these tissues remains unclear. Only recently have V1bR transcripts as well as V1bR immunoreactive cell bodies been found in the rat brain, including in 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 V1bR distribution has not been mapped by receptor autoradiography due to the lack of specific radiolabeled ligands. Fortunately, the development of a V1bR knockout (V1bRKO) mouse has offered critical insight into the role of V1bR in the mouse brain (below).

4.1.2 Regulation

Within the CNS, V1aR transcription and translation are sensitive to gonadal steroids. In the photoperiodic Syrian and Siberian hamsters, exposure to short "winter-like" photoperiods results in dramatic reductions in V1aR binding within brain areas associated with the neural regulation of social behavior (Dubois-Dauphin et al., 1994; Caldwell and Albers, 2003, 2004b). Likewise, gonadectomy and lactation can decrease V1aR mRNA and receptor binding within the hypothalamus (Johnson et al., 1995; Delville et al., 1995; Young et al., 2000). In young rats, estrogen increases V1aR mRNA in the preoptic area of the hypothalamus (Funabashi et al., 2000). Castration leads to reduced binding in the pudendal nuclei of L5/L6 (Tribollet et al., 1997). While it is clear that gonadal hormones can affect V1aR transcription and translation within specific parts of the brain, the mechanisms underlying these changes remain unknown. Presumably, gonadal steroids could directly affect V1aR transcription through response elements, but none have been identified yet. There do, however, appear to be putative GREs within the 5′-flanking region of the V1aR gene. In rats, adrenal steroids can affect V1aR mRNA expression and V1aR binding within the LS and BNST (Watters et al., 1996). There is still much work to do to understand the regulation of V1aR transcription and its complex relationship with steroid hormones.

A recent study found that expression of the V1aR increased after traumatic head injury (Szmydynger-Chodobska et al., 2004). The increase was observed in astrocytes of the damaged frontal cortex, and the receptor was observed to move from the cell body to processes with time. It is interesting to speculate as to whether VP plays a role in cerebral edema that may accompany brain trauma.

Some very provocative work has focused on interspecies and individual variations in the V1aR promoter of voles. Across vole species there are profound differences in social structure and behavior. Prairie voles (*Microtus ochrogaster*) and pine voles (*Microtus pinetorum*) tend to be social and monogamous while montane voles (*Microtus montanus*) and meadow voles (*Microtus pennsylvanicus*) tend to be asocial and polygamous. These social behaviors are mediated, at least in part, by VP action on the V1aR (Winslow et al., 1993; Wang et al., 1994; Cho et al., 1999; Young et al., 1999; Liu et al., 2001). There are striking differences in the distribution and density of V1aR between these species (Young et al., 1997b, 1999). Within the promoter region of the V1aR gene of the prairie and pine voles, there is an approximately 400-bp sequence of repetitive DNA, known as a microsatellite sequence, which is absent from the promoter region of the V1aR gene in the montane and meadow voles. The length of this microsatellite sequence shows a correlation with V1aR expression patterns and ultimately behavior (Hammock and Young, 2002; Hammock et al., 2004). We will come back to the role of this microsatellite polymorphism in the mediation of behavior later in this chapter.

While V1bR has only been described relatively recently, there has been some work examining its regulation in the pituitary. In the rat, pituitary expression of V1bR appears to be positively regulated by corticosteroids and perhaps by VP (Rabadan-Diehl et al., 1997; Rabadan-Diehl and Aguilera, 1998). V1bR expression appears to increase or decrease depending on the stressor (Rabadan-Diehl et al., 1995; Aguilera and Rabadan-Diehl, 2000; Qahwash et al., 2002). In the rat, there are AP-1 and AP-2 sites and a GRE in the 5′-flanking region. In humans there is a half-palindromic sequence for estrogen, a cAMP response element, and a GRE (Aguilera et al., 2003). The V1bR promoter also contains a GAGA box essential for expression (Volpi et al., 2002). The V1bR 5′-untranslated region contains small expressed minicistrons or open reading frames that appear to inhibit V1bR expression posttranscriptionally as well as an internal ribosomal entry site that may be uncovered when increased expression is desired (Nomura et al., 2001; Aguilera et al., 2003). How these regulatory elements all interact to regulate the V1bR gene is still being investigated (Volpi et al., 2004b). Nothing is known about V1bR regulation in the brain proper and will likely be a fruitful field for investigation.

4.2 The Oxytocin Receptor

Physiologically and behaviorally, OT regulates reproduction across species, from its peripheral effects on milk ejection and uterine contractions to its central effects on sexual behavior, maternal behavior, and pair

bonding. A single OT receptor (OTR) appears to transduce the actions of OT. This receptor was first isolated and identified by Kimura and colleagues in 1992.

The OTR is also a member of the G-protein-coupled receptor family. Like other members of this family, the OTR contains seven transmembrane domains and is similar in structure to the VP receptors. The OTR is also coupled to $G_{\alpha q/11}$ GTP-binding proteins and $G_{\beta\lambda}$ (Ku et al., 1995; Gimpl and Fahrenholz, 2001; Zingg and Laporte, 2003) to cause the hydrolysis of phosphatidylinositol and act through pathways similar to that of the V1Rs.

4.2.1 CNS Distribution

Initially, the location of OTR expression was determined by receptor autoradiography, using a potent and specific ^{125}I-labeled antagonist (Kremarik et al., 1993; Veinante and Freund-Mercier, 1997). In the rat, OT binding is found in numerous regions, especially in the hippocampal formation (ventral subiculum particularly), LS, central amygdala (CeA), olfactory tubercle, accumbens nucleus shell, dorsal caudate-putamen, BNST, MeA, and ventromedial hypothalamus (VMH). Binding in the spinal cord is light and confined to the superficial dorsal horn (Tribollet et al., 1997).

Hybridization histochemistry reveals OTR transcripts in many areas of the rat CNS, including main and accessory olfactory bulbs, neocortical layers II and III, piriform cortical layer II, hippocampal formation, olfactory tubercle, BNST, medial habenula, VMH, PVN, and SON. Expression is lower in the midbrain, pons, and medulla (Vaccari et al., 1998). Recently, an OTR–*lacZ* reporter mouse has shown additional OTR gene expression in the medial septum, parts of the amygdala and mammillary nuclei, and some brainstem nuclei (Gould and Zingg, 2003).

The distribution of the OTR is highly species specific, as is elegantly illustrated in receptor binding differences between two closely related species of voles, the polygamous montane vole and the monogamous prairie vole (Insel and Shapiro, 1992; Insel et al., 1997). Differences in the distributions of the OTRs have also been shown among mice, rats, voles, hamsters, and guinea pigs (Insel et al., 1993). These differences in OTR distribution across species are thought to confer differing behavioral phenotypes, as discussed below.

4.2.2 Regulation

In a variety of species, both transcription and translation of the OTR gene are sensitive to gonadal steroids. In rats, OTR binding and mRNA levels in the brain and myometrium of the uterus are increased with estradiol and testosterone treatment (Tribollet et al., 1990; Stevenson et al., 1994; Larcher et al., 1995; Breton and Zingg, 1997). Curiously, estrogen tremendously increases the expression of the OTR in the kidney (Ostrowski et al., 1995; Breton et al., 1996). Castration and inhibition of estrogen synthesis results in a decrease in OTR binding in the rat brain (Tribollet et al., 1990). OTR within the VMH, an important nucleus for the regulation of sex behavior, has been the focus of intense study. OTR expression within the VMH of both males and females is particularly sensitive to gonadal steroids (de Kloet et al., 1985, 1986; Coirini et al., 1989; Johnson et al., 1991; Bale and Dorsa, 1995; Bale et al., 1995; Quinones-Jenab et al., 1997). Interestingly, the mouse is the only known species in which there is a complete palindromic ERE in the promoter of the OTR gene (Bale and Dorsa, 1997); rats and humans have only half-palindromic EREs (Inoue et al., 1994; Rozen et al., 1995). It does appear likely, however, that estrogen can act on the half-palindromic EREs with low affinity (Sanchez et al., 2002). The OTR gene has several other response elements in its promoter, including an interleukin response element, a cAMP response element, and AP-1, AP-2, AP-3, and AP-4 sites (Rozen et al., 1995; Bale and Dorsa, 1998; Gimpl and Fahrenholz, 2001). While there seems to be ample information on potential modulators of OTR synthesis, there is much work to do to understand their interaction with one another. For a more detailed description of the OTR system, there are several excellent reviews including ones by Gimpl and Fahrenholz (2001), Kimura et al. (2003), and Zingg and Laporte (2003).

5 Behavioral and Physiological Effects of Vasopressin and Oxytocin

Across species OT facilitates bonding behaviors between offspring and parents and between males and females, whereas VP appears to be more involved in the regulation of aggression and male parental care. Understanding the involvement of OT and VP in the regulation of sexual and social behaviors has been, and continues to be, the source of exciting research in behavioral neuroendocrinology. Our understanding of how OT and VP systems interact with one another and with other neurotransmitter systems to affect behavior is still in its infancy. However, some recent work has begun to shed some light on their profound and lasting effects on behavior across species. The use of transgenic animal models and viral vectors has moved the field forward and provided valuable insight into the individual roles of OT and VP in the mediation of behavior. This section will survey past and current findings on the roles of OT and VP in the regulation of a variety of behaviors. A summary of this section can be found in ❯ *Table 25-3*.

Table 25-3
Summary of the behavioral effects of OT and VP

Behavioral classes	Behaviors	Effects of OT	Effects of VP
Reproductive behaviors	Maternal behavior	⇑ when injected ICV and into the MPOA	Maternal aggression impaired in V1bRKO mice
	Female sexual behavior	⇑ when injected into the MPOA-AH and VMH	No known effect
	Male sexual behavior	⇑ in erection when injected ICV	No known effect
Social behaviors Aggression	Female aggression	⇑ when injected into the MPOA-AH (hamsters) and CeM (rats).	Maternal aggression impaired in V1bRKO mice
	Male aggression	⇔ conflicting reports	⇑ when injected into the AH and LS impaired in V1bRKO mice
Social memory	Social recognition	⇔ conflicting reports, but is impaired in OTKO mice	impaired in V1aRKO and V1bRKO mice
	Partner preference	⇑ when injected ICV in females and in males following neonatal exposure	⇑ when injected ICV in male prairie voles; dependent on V1aR distribution
Other Behavioral and Physiological Effects	Scent marking and grooming	⇑ when injected ICV in males and females (rats)	⇑ when injected into the MPOA-AH (hamsters)
	Anxiety and depression	⇓ in anxiety when injected ICV in females	Correlation in VP release from the PVN and ⇑ in anxiety (rats); V1aRKO mice show reduced anxiety
	Learning and memory	⇑ in spatial learning in female; acts as an amnestic in some tests	⇑ in spatial learning when injected into the ventral hippocampus of scopolamine-treated male rats
	Fever	No known effect	⇓ when infused into the LS

5.1 Reproductive Behaviors

5.1.1 Maternal Behavior

The term "maternal behavior" encompasses a spectrum of behaviors describing the care of offspring by a female of a species. In a variety of species, OT is important for the regulation of maternal behaviors. In rats,

OT infused intracerebroventricularly (ICV) or directly into the medial preoptic area (MPOA) can stimulate maternal behavior (Pedersen and Prange, 1979; Pedersen et al., 1982; Fahrbach et al., 1985; Pedersen, 1997). Similarly, in mice OT injected ICV increases maternal behavior (McCarthy, 1990). Lesions of OT-producing neurons in estrogen-primed virgin female rats inhibit maternal behavior (Insel and Harbaugh, 1989), and centrally administered OT antisera or OTR antagonists reduce maternal behaviors (Pedersen et al., 1982; Fahrbach et al., 1985; van Leengoed et al., 1987). In sheep, high levels of OT within the limbic system are important for maternal behavior and OT injected ICV can induce maternal behavior in sexually naïve animals. It may be that in sheep OT is a more potent regulator of maternal behavior because its effects are faster acting than those seen in rodents (Keverne and Kendrick, 1994; Kendrick et al., 1997).

While OT can directly influence maternal behavior, estrogen also interacts with the OT system. Estrogen can affect the transduction of OT signals by altering OTR transcription and translation. As estrogen concentrations change across the estrous cycle and during pregnancy, there are coinciding changes in OTR expression. In rats, as estrogen levels increase following parturition, there is an activation of c-fos and fos-B in OTR expressing cells within the MPOA, BNST, and amygdala (Lin et al., 2003). Exogenous estrogen treatment increases OTR density within the MPOA, resulting in the support of OT mediated maternal behaviors (Patchev et al., 1993; Young et al., 1997a). Estrogen induced OTR in the LS, CeA, PVN, and BNST can affect grooming and licking behavior in rats, both of which are part of the normal repertoire of maternal behaviors (Champagne et al., 2001; Francis et al., 2002). In light of these data, it is obvious that OT is a regulator of maternal behavior in rats. Surprisingly, mice with a disruption of their OT gene (OTKO) display normal maternal behaviors (Winslow and Insel, 2002). Oxytocin knockout (OTKO) mice show normal parturition, licking, and grooming behaviors, but do not lactate. The conflicting results between in vivo pharmacological studies and the OTKO studies may be due to a developmental compensation in OTKO mice. This idea is supported by a recent study that found that within the VMH of OTKO mice, VP can act on the OTR (Ragnauth et al., 2004). If VP is substituting for OT in OTKO mice, it would then explain the presence of normal maternal behavior in OTKO mice.

5.1.2 Female Sexual Behavior

OT within the CNS also regulates female sexual receptivity across species. In female Syrian hamsters, OT microinjected into the medial preoptic area-anterior hypothalamic continuum (MPOA-AH) or into the VMH induces sexual responsiveness, as measured by the duration and frequency of sexual receptivity, i.e., lordosis behavior (Whitman and Albers, 1995). In rats, OT injected into the MPOA-AH or medial basal hypothalamus in combination with estrogen or estrogen conjugated to bovine serum albumin (so it cannot pass through the cell membrane and into the cell to act on classical estrogen receptors), increases sexual receptivity (Caldwell et al., 1989; Caldwell and Moe, 1999). Conversely, OTR antagonists injected ICV in rats or into the MPOA-AH of Syrian hamsters reduce sexual receptivity (Benelli et al., 1994; Whitman and Albers, 1995). Also, when infused into the VMH of female rats, antisense oligonucleotides against OTR prevent female sexual receptivity (McCarthy et al., 1994). Aside from its regulatory effects on lordosis, OT injected into the MPOA-AH of Syrian hamsters increases their ultrasonic vocalizations, an important component of sex behavior (Floody et al., 1987). Interestingly, low concentrations of OT infused into the lateral ventricles can actually reduce lordosis, suggesting that the effects of OT on receptivity do not follow a simple dose–response curve (Schulze and Gorzalka, 1992). Again surprisingly, female (and male) sexual behavior is not significantly affected in OTKO mice (Nishimori et al., 1996; DeVries et al., 1997). Whether this is permitted through compensation and/or redundancy of this vital behavior remains unanswered.

5.1.3 Male Sexual Behavior

In males, OT neurons originating from the PVN and projecting to extrahypothalamic brain areas and spinal cord are involved in aspects of male sexual behavior, including copulation and erection. Humans show increases in plasma OT at ejaculation (Carmichael et al., 1987; Murphy et al., 1987) and in male rats, OT is

elevated following exposure to females (Hillegaart et al., 1998). At least in rodents, these increases in OT correlate with the intensity of copulation (Hillegaart et al., 1998). OT administered centrally can induce penile erection that castration or hypophysectomy can abolish (Argiolas et al., 1985; Argiolas, 1999). OT antagonists injected ICV reduce mounts and intromissions, and ejaculations are completely abolished (Argiolas et al., 1988). One of the critical sites for the neural regulation of erection is the PVN. Lesions of OT neurons of the PVN prevents erection and injections of OTR antagonists into the lateral ventricles also prevent erection (for review see Argiolas, 1999; Andersson, 2001; Argiolas and Melis, 2004). Even in amphibians such as the rough-skinned newt (*Taricha granulosa*), clasping behaviors are affected by the OT homologue AVT (Moore, 1983), suggesting that OT is important to displays of sexual behavior across species.

5.2 Social Behaviors

5.2.1 Aggression

In a variety of species, aggressive behavior is important to the development and maintenance of social structures. Defense of territory, protection of young, formation of social hierarchies, and competition for mates are just some of the reasons why animals display aggressive behaviors. In general, males are more aggressive than females, though females often show increased aggression during pregnancy and in the subsequent postpartum period. Recently, interest in understanding the neural underpinnings of violent and aggressive behavior has increased. Aggression is notoriously difficult to study, but the use of specific pharmacological agents and transgenic mouse models have aided in our understanding of the neural regulation of aggression and have shown that OT and VP have important roles in the regulation of aggression across species.

5.2.1.1 Female Aggression In many mammalian species, females are only aggressive during pregnancy and following parturition. There are, however, notable exceptions in some mammalian species, such as spotted hyenas (Holekamp and Smale, 2000) and Syrian hamsters (Payne and Swanson, 1970). In female Syrian hamsters, injections of OT into the MPOA-AH can reduce the duration of aggressive behavior directed toward a nonaggressive, female intruder (Harmon et al., 2002a). Even in female voles, OT injected ICV can decrease male-directed aggression (Bales and Carter, 2003b). Thus, it appears that OT can reduce nonmaternal aggressive behaviors.

The role of OT in the regulation of maternal aggressive behavior remains somewhat murky. While OT can facilitate maternal aggression in female Syrian hamsters when microinjected into the amygdala (Ferris et al., 1992), OT antagonists injected into the CeM of rats also increases maternal aggression (Lubin et al., 2003). Reduction of OT using antisense oligonucleotides and lesions of the PVN also reduce maternal aggression in rats (Giovenardi et al., 1998). Most of the studies that have implicated OT in the mediation of maternal aggression have used gestational cocaine treatment. Gestational cocaine treatment reduces OT and OTR in several brain areas (Johns et al., 2004). As a result, there is a subsequent increase in maternal aggression thought to be due in part to these changes in the OT neurocircuitry (Johns et al., 1997; Elliott et al., 2001). While OTKO mice would seem the obvious model in which to examine OT regulated maternal aggression, to our knowledge maternal aggression has not been examined in OTKO mice. However, the results of studies using these mice might be difficult to interpret in light of the recent work suggesting that VP can act directly on the OTR in OTKO mice (Ragnauth et al., 2004).

5.2.1.2 Male Aggression VP has been implicated in the modulation of male aggressive behavior across species. In birds, fish, rodents, and primates, VP or nonmammalian VP homologues can affect aggressive behavior (Ferris and Potegal, 1988; Winslow and Insel, 1991b; Goodson and Adkins-Regan, 1999; Semsar et al., 2001). Some neurocircuitry underlying aggressive behavior has been described. In Syrian hamsters, the anterior hypothalamus (AH), which has reciprocal connections with the ventrolateral hypothalamus (VLH), MeA, and BNST, is an important site in the regulation of aggressive behavior (Delville et al., 2000)

and will be discussed in more detail below. In rats and mice, gonadal steroid-dependent VP projections from the BNST and the MeA to the LS (De Vries et al., 1984, 1985; Van Leeuwen et al., 1985; Miller et al., 1992) have been implicated in the modulation of aggressive behavior (Scordalakes and Rissman, 2004). In rats and prairie voles, VP injected into the LS can induce agonistic behavior (Koolhaas et al., 1991; Winslow et al., 1993; Wang et al., 1994). However, in wild-type (WT) rats there is a negative correlation between reduced VP in the LS and aggressive behavior (Everts et al., 1997). While the exact role of VP in the LS is not certain, it may be that the LS regulates the emotional aspects of aggressive behavior (Desmedt et al., 1999; Everts and Koolhaas, 1999).

Aggressive behavior in Syrian hamsters is particularly well-studied (Ferris and Delville, 1994). Microinjections of specific V1aR antagonists into the VLH and the AH can reduce agonistic behavior (Ferris and Potegal, 1988; Delville et al., 1996). Interestingly, only in socially dominant animals do microinjections of VP into the AH facilitate offensive aggressive behavior (Ferris et al., 1997; Caldwell and Albers, 2004a). This seems to be a common theme across species; while VP is an important modulator of aggressive behavior, its effects are specific to the social status of the animal. For instance, only in "dominant" squirrel monkeys does an ICV injection of VP increases aggression (Winslow and Insel, 1991b). Even conditions such as housing, which are known to affect social status (Grelk et al., 1974), alter VP neurocircuitry by causing a redistribution of V1aR. Syrian hamsters that are singly housed show more V1aR binding in several brain areas compared with group-housed males (Smith et al., 2001) and tend to be more aggressive (Brain, 1972). There is more VP-ir in the LS of mice bred for short-attack latencies, and more VP-ir in the BNST of mice bred for long-attack latencies (Compaan et al., 1993). While it is not surprising that the brain of a dominant animal differs from that of a subordinate animal, understanding this plasticity will continue to be an exciting area of research.

Until recently, most work examining the regulation of aggressive behavior by VP assumed action via the V1aR. However, aggression studies using V1bR knockout (KO) mice suggest that normal displays of aggressive behavior require a functional V1bR. V1bRKO mice show significant reductions in aggressive behavior as they do not attack intruders in either neutral arena or resident–intruder behavioral models (Wersinger et al., 2002). In contrast, V1bRKO mice show normal predatory aggression (Wersinger et al., 2003), suggesting that the V1bR is critical for social forms of aggressive behavior. V1bRKO mice also have reduced social motivation and spend equal time investigating clean bedding or bedding soiled either by females or males (Wersinger et al., 2004). A recent study in Syrian hamsters supports the findings of the V1bRKO studies. Hamsters administered a selective V1bR antagonist orally showed marked reductions in offensive aggression, and the authors also suggested that the V1bR may be involved in the behavioral response to stress (Blanchard et al., 2005). While the distribution of V1bR binding in mice and hamsters has yet to be determined, the behavioral findings indicate that further study of the V1bR and its role in aggressive behavior will be enlightening.

The role of OT in the mediation of aggressive behavior in males is conflicting. In OTKO mice, one group reported increases in aggressive behavior in male OTKO mice (Winslow et al., 2000) while another group reported decreases in aggressive behavior (DeVries et al., 1997; Young III et al., 1998). Since two different groups generated the OTKO mice used in the above studies and the methods employed were not identical, the precise role of OT in the modulation of male aggressive behavior remains unknown.

5.2.2 Social Memory

Formation of social bonds between individuals is important for the survival of many species. Throughout the animal kingdom successful reproduction requires interactions between individuals. Whether a species is social or asocial, monogamous or polygamous, the formation of social bonds is critical. Social recognition is a specific type of memory on which animals rely to recognize familiar from unfamiliar conspecifics, while partner preference refers to an individual's social attachment to a conspecific. Classical pharmacological studies as well as transgenic animal studies have been successful in deepening our understanding of the neural regulation of social recognition. However, the use of nontraditional model species, like voles, has provided valuable insight into the molecular basis of partner preference. This section will review some of

the more recent work in the field of social recognition and partner preference, although, the interested reader should refer to several recent reviews on the topic (Bielsky and Young, 2004; Insel and Fernald, 2004; Keverne and Curley, 2004; Young and Wang, 2004).

5.2.2.1 Social Recognition Although the sensory modality by which individuals recognize one another may differ among species, the ability to recognize individuals is essential for survival. Whether an animal is recognizing a parent, an offspring, a potential mate, or an aggressor, social recognition is important for displaying appropriate behaviors. In humans and nonhuman primates, social recognition depends mostly on visual and auditory cues, whereas in other mammals such as rodents, olfactory and pheromonal cues provide the most accurate information about others. The processing of the olfactory information relies upon OT and VP to aid in the formation of social memories. An in depth review of the neural regulation of social recognition can be found in a recent article by Bielsky and Young (2004).

The evidence that VP is critical for social recognition is compelling. Since the LS receives projections from the MeA and BNST (De Vries and Buijs, 1983; Caffè et al., 1985) and contains VP receptors (Johnson et al., 1993), it has been the focus of studies on social recognition. Injections of VP into the LS can enhance social recognition (Dantzer et al., 1987). Conversely, V1aR antagonists or antisense oligonucleotides can inhibit or reduce social recognition (Landgraf et al., 1995). Social recognition is improved when V1aR expression is artificially increased in the LS of rats using a viral vector expressing a vole V1aR gene (Landgraf et al., 2003).

The use of V1aRKO and V1bRKO mice has provided valuable insight into the role of VP in the regulation of social recognition. V1bRKO mice do not show normal chemoinvestigatory behaviors and have mild impairments in social recognition (Wersinger et al., 2002). V1bRKO mice do have normal olfaction, and there are no known differences in fos-like immunoreactivity between V1bRKO mice and WT mice following exposure to the odor of a conspecific male. These results suggest that V1bRKO mice process initial olfactory information normally (Wersinger et al., 2002). Interestingly, V1bRKO females do not show pregnancy block when exposed to a novel male (the Bruce effect); they remain pregnant, as if they do not recognize a stranger mouse as "new" (Temple et al., 2003). Studies utilizing an operant conditioning task to examine olfactory discrimination have confirmed that V1bKO mice can discriminate between male and female urine even though they do not spend more time investigating female than male bedding. It has been suggested that they lack normal social motivation based on these data. They can distinguish male from female, but it is as if they just do not care; therefore, they do not behave in a socially appropriate manner (Wersinger et al., 2002, 2004). Further exploration of this hypothesis will be interesting. It may be that V1bR and V1aR differentially regulate very specific aspects of social recognition. Recent studies examining V1aRKO mice suggest that they have much more profound impairments in social recognition than do V1bRKO mice (Bielsky et al., 2003). Upon repeated exposure to the same female, V1aRKO male mice fail to reduce their olfactory investigation. Since studies of V1aRKO mice show normal olfactory investigation and habituation, the authors suggest that the V1aR is critical for the appropriate processing of olfactory cues (Bielsky et al., 2003).

The effects of OT on social recognition are more complex. There are conflicting reports in rats, where OT has been shown to both facilitate and inhibit social recognition (Popik et al., 1996; Dluzen et al., 1998). While high concentrations of OT injected into the LS enhance social recognition in the rat, low doses of OT injected into the MPOA are more effective (Popik and Van Ree, 1991). Interestingly, OTR antagonists infused into the LS or MPOA do not block social recognition (Popik et al., 1996). Possible explanations for the discrepancies between agonist and antagonist studies include, the use of antagonists that were not highly selective and that OT could affect social recognition via V1 receptors.

While studies in rats may not clearly point to OT for the regulation of social recognition, this is not the case in mouse studies. OTKO mice do not display normal social recognition (Ferguson et al., 2000), and comparisons between OTKO and estrogen receptor alpha and beta KO mice suggest the effects of OT on social recognition are gonadal-steroid-dependent (Choleris et al., 2003). The differences in social recognition between WT and OTKO mice are likely due to differences in the processing of olfactory information. OTKO mice have decreased c-fos activation within the MeA, BNST, and MPOA (Ferguson et al., 2001). All three of these areas process olfactory information downstream of the accessory olfactory bulb (Meredith,

1991). In fact, if OT is injected prior to a social encounter in OTKO mice, either ICV or intracerebrally directly into the CeA, social recognition is fully restored. Conversely, ICV injections of OT antagonists into WT mice reduce social recognition. OT has no effects on social memory if it is administered after the encounter (Ferguson et al., 2001), suggesting that OT is critical for memory acquisition rather than memory recall. Another example of the impaired social recognition is displayed by OTKO mice, which when exposed to their first mate or a novel mate (Bruce effect), do not remain pregnant (Temple et al., 2003). Choleris et al. (2004) have proposed a four-gene micronet for the regulation of social recognition in mice that includes estrogen receptor alpha, estrogen receptor beta, OT, and the OTR, although the reduced social recognition in the V1aRKO and V1bRKO suggests a much more complicated scenario in which numerous genes are involved.

5.2.2.2 Pair Bonding Pair bonding is the monogamous relationship between sexual partners. Pair bond formation is studied by measuring an animal's partner preference (the amount of time individuals spend with their respective partners versus strangers). While monogamy is rare among mammalian species, being found in fewer than 5% of species (Kleiman, 1977), understanding its neural basis continues to be an exciting area of research. One of the questions driving this field of research is why does one species demonstrate monogamy while another species does not?

The first work linking OT and VP to partner preference was completed in prairie voles (Carter et al., 1992; Winslow et al., 1993). Voles have continued to be the model species of choice since there are monogamous as well as polygamous species within the genus *Microtus.* As mentioned previously, prairie and pine voles tend to be social and monogamous while montane and meadow voles tend to be asocial and polygamous. The facilitation of partner preference by OT and VP is sex specific, with OT being more important in females and VP in males. Female prairie voles administered OT ICV develop a partner preference more rapidly, while an OT antagonist given prior to mating can block partner preference formation (Williams et al., 1994; Insel and Hulihan, 1995; Cho et al., 1999). In male prairie voles, VP and V1aR antagonists facilitates and inhibit formation of partner preference, respectively (Winslow et al., 1993; Cho et al., 1999). The reason for this sex difference remains poorly understood since there are no discernable differences in OTR and V1aR densities and distributions between male and female prairie voles. A recent study has suggested that neonatal exposure to OT can increase partner preference in adult males (Bales and Carter, 2003a).

While the exact basis for the sex difference remains to be determined, the reasons why OT and VP have differential effects in monogamous versus polygamous voles is better understood. Polygamous voles have a lower density of OTR in the caudate-putamen and nucleus accumbens compared with monogamous voles (Insel and Shapiro, 1992). They also have lower densities of V1aR in the ventral pallidum, MeA, and thalamus (Insel et al., 1994). Most of the aforementioned areas are a part of the mesolimbic dopamine reward pathway, suggesting that in certain species, pair bonding may be reinforcing (Insel and Young, 2001; Insel, 2003). This hypothesis is supported by studies that have shown that dopamine acting through D_2 receptors within the nucleus accumbens is necessary for partner preference formation (Gingrich et al., 2000; Aragona et al., 2003a, b; Liu and Wang, 2003).

There is increasing support for the idea that animals are polygamous or monogamous partly because of differences in the distribution of OT and VP receptors. Transgenic mice that express the prairie vole V1aR gene in a prairie vole-like pattern show increased affiliative behaviors when VP is injected ICV (Young et al., 1999). VP induces increased partner preference in polygamous meadow voles in which the prairie vole V1aR is overexpressed in the ventral pallidum via a viral vector (Lim et al., 2004b). The molecular basis of pair bonding, as reflected in the distribution patterns of V1aR expression, has been attributed to differences in microsatellite sequence length in the 5′-UTR region of the V1aR coding sequence. These microsatellite sequences are repetitive, unstable (Li et al., 2004), and can modulate gene expression levels and regional distribution (Hammock and Young, 2002; Hammock et al., 2004). It is thought that microsatellite sequences are more susceptible to mutation and may represent a mechanism for the generation of individual variation within a species (Hammock and Young, 2002; Phelps and Young, 2003; Lim et al., 2004b). For a more in depth review of pair bonding and its genetic regulation, see articles by Insel (2003), Young and Wang (2004), Aragona and Wang (2004), and Lim et al. (2004a).

5.3 Other Behavioral and Physiological Effects

5.3.1 Scent Marking and Grooming

The most extensive work examining the role of VP in scent marking has been done in Syrian hamsters. Syrian hamsters have a specialized form of scent marking known as flank marking. Flank marking is displayed for several reasons including marking territory, attracting a mate, and informing others of their dominance status (Johnson, 1973). In 1984, Ferris and colleagues made the serendipitous finding that flank marking was induced when VP was injected unilaterally into the MPOA-AH (Ferris et al., 1984). The MPOA-AH is thought to be the critical regulatory site for this behavior, because lesions of the MPOA-AH, but not other sites, result in reductions in flank marking (Ferris et al., 1986). Not only does VP induce flank marking, but also does so in a dose-dependent manner. Concentrations ranging from 0.09 μM to 90 μM induce from 3 to 80 flank marks, respectively, within a 10-min period (Ferris and Potegal, 1988). The facilitation of flank marking is also testosterone-dependent. When hamsters are castrated, there are significant declines in flank marking that can be restored following treatment with exogenous testosterone (Albers et al., 1988). The effects of VP on flank marking are mediated primarily through V1aR. Specific antagonists for the V1aR have been shown to significantly reduce levels of VP-induced flank marking and odor-induced flank marking (Ferris et al., 1985, 1988; Albers et al., 1986). In female Syrian hamsters, OT has been found to facilitate flank marking when injected into the MPOA-AH of socially dominant female hamsters. Similar to what has been found in VP-facilitated aggression, social experience is critical for OT's effects on flank marking as socially naïve females show no increases in flank marking compared with controls (Harmon et al., 2002b).

The only other species in which VP has been shown to have an effect on scent marking is in male squirrel monkeys. When VP is administered centrally during a social separation test, squirrel monkeys will increase their scent marking and grooming behavior (Winslow and Insel, 1991a). In other species, VP tends to affect grooming. In mice, VP injected in the MPOA can induce grooming (Meisenberg and Simmons, 1982; Lumley et al., 2001). In rats, OT, rather than VP, given ICV can induce self-grooming in males and females and this effect of OT is inhibited by an OTR antagonist (Delanoy et al., 1978; Caldwell et al., 1986; Drago et al., 1986, 1991). OT-induced grooming has even been used as a way to measure the sensitivity of OT receptors in OTKO mice. OTKO mice given OT ICV show increased grooming behavior compared with WT controls, suggesting that in OTKO mice, the OTR is more responsive to OT (Amico et al., 2004).

5.3.2 Anxiety and Depression

Anxiety[1] is one of the behavioral manifestations of stress. While OT has been consistently linked to anxiety, the role of VP has been much less clear. However, there is increasing evidence that both OT and VP are important in the modulation of anxiety in a variety of species. In two rat lines bred for high- or low-anxiety-related behavior, there is a correlation between increased VP mRNA and VP release from the PVN and the high-anxiety phenotype (Wigger et al., 2004). The increase in VP in the PVN has been attributed to an overexpression of VP due to an impaired repression of the VP promoter (Murgatroyd et al., 2004). These studies suggest that VP release from the PVN may be important to the regulation of anxiety in males. The LS is also an area demonstrated to be involved in the regulation of anxiety. Lesions of the LS and V1aR antisense oligonucleotides infused into the LS result in decreases in anxiety-like behaviors in rats (Landgraf et al., 1995; Menard and Treit, 1996). Interestingly, disruption of the V1bR in mice has not been found to affect anxiety-like behaviors (Wersinger et al., 2003). However, V1aRKO males are significantly less anxious than WT males (Bielsky et al., 2003). Therefore, it may be that the V1aR is the more critical receptor for the

[1] When anxiety is mentioned in relation to animals, one is really referring to behaviors that are affected with a similar rank order of potency by agents ("anxiolytics") that are used to treat anxiety in humans. Similar caveats are applied when anthropomorphizing any human mental disturbance.

effect of VP on anxiety. The V1bR antagonist SSR149415 shows weak anxiolytic activity but stronger activity indicative of antidepressant potential in rats (Griebel et al., 2002). This selective V1bR antagonist, when injected into the LS of rats, has antidepressant-like effects on their behavior (Stemmelin et al., 2005). Finally, a single-nucleotide polymorphism in the V1bR gene in humans has been reported to have a protective effect on recurrent major depression (van West et al., 2004).

In birds, OT injected ICV decreases food intake and pecking frequency, suggesting that their general state of arousal and anxiety may be increased (Jonaidi et al., 2003). In rats and mice, OT has been characterized as an anxiolytic (Windle et al., 1997; Neumann et al., 2000; Bale et al., 2001; McCarthy et al., 1996). During the perinatal period, rats show increased anxiety-like behavior, compared with virgin female controls. These behaviors can be enhanced following treatment with an OTR antagonist. However, in virgin female and male rats, treatment with the OTR antagonist has no effect on anxiety-like behaviors (Neumann et al., 2000; Neumann, 2001). Female OTKO mice have higher level of anxiety-like behavior than WT animals, and this anxiety-like behavior can be decreased by ICV administration of OT (Mantella et al., 2003). In contrast to females, male OTKO mice display less anxiety-like behavior (Winslow et al., 2000; Mantella et al., 2003). Overall, it appears that OT may be more important to the regulation of anxiety in females and VP in males. It will be interesting to find out if the regulation of anxiety-like behaviors is truly sexually dimorphic, using two completely different neuroanatomical circuits, or if the main difference lies in the type of neuropeptide and receptor.

5.3.3 Learning and Memory

Throughout the 1960s and 1970s, David De Wied dominated this field by examining the effects of VP and OT on learning and memory. His earliest study in 1965 found that in rats, removal of the posterior pituitary impaired active avoidance shuttlebox performance (De Weid, 1965). He subsequently showed that this impairment is improved by treatment with VP (De Weid, 1976). Not only did he find that VP facilitates memory processing, but that its effects are more robust during consolidation and retrieval rather than during learning. By chemically altering VP, he was able to determine which parts of the peptide (VP and OT "metabolites") were biologically active in the aspects of learning and memory he studied (De Weid et al., 1993). He also showed that OT acts as a natural amnestic agent by impairing memory consolidation and retrieval (De Weid et al., 1991). De Wied's theories on learning and memory have been challenged. Sahgal and colleagues propose that both central and peripheral VP increase baseline arousal, which in turn alters learning and memory (Sahgal, 1984; Sahgal and Wright, 1984). While this argument has yet to be settled, especially with regard to the existence of VP and OT metabolite receptors, there is still ongoing research examining the roles of OT and VP on learning and memory, including spatial memory.

While it is known that rodents that give birth have improved spatial memory, only recently has it been shown that OT has a role. In a study by Tomizawa and colleagues (2003), OT given ICV to mice that have never been pregnant increased spatial learning (reference memory only with no effect on working memory). Conversely, they showed that an OTR antagonist administered ICV to females that had delivered several litters inhibited spatial learning. Further, they suggest that OT improves spatial learning by stimulating long-lasting, long-term potentiation and phosphorylation of the cAMP responsive element binding protein in the hippocampus (Tomizawa et al., 2003). It will be interesting to see if these hypotheses are confirmed and expanded to include males.

Some studies in male rats and mice have suggested that VP acting on the V1aR is important for normal spatial memory. VP microinjected into the ventral hippocampus of rats can improve scopolamine-induced impairment of spatial memory (Fujiwara et al., 1997). Conversely V1aR agonists enhance spatial memory (Mishima et al., 2003), whereas V1aR antagonists, but not V2 antagonists, suppress this effect (Mishima et al., 2001; Egashira et al., 2004). Recent work examining spatial memory in V1aRKO male mice has supported the idea that VP may be important to spatial memory. V1aRKO mice show more errors in the eight-arm radial maze than do WT mice (Egashira et al., 2004). Interestingly, no impairments are seen in the Morris water maze. The authors suggest that this is because the eight-arm radial maze is also testing working memory, and it is this aspect of memory that may be affected by the lack of V1aR (Egashira et al.,

2004). To date no deficits in spatial memory have been observed in V1bRKO (Wersinger et al., 2002; Egashira et al., 2004).

5.3.4 Fever

During late pregnancy and in newborns, there is a natural suppression of fever concurrent with increases in circulating VP (Alexander et al., 1974; Stark et al., 1979). Studies examining circulating VP find no effect on fever reduction (antipyresis) (Cooper et al., 1979). However, VP infused into the septal area of the brain in several species reduces fever (Cooper et al., 1979; Naylor et al., 1985; Cooper et al., 1987). Fever is also reduced when the BNST is electrically stimulated, resulting in the release of VP into the septum (Naylor et al., 1988). These effects are thought to be mediated through the V1aR based on agonist/antagonist studies (Cooper et al., 1987; Landgraf et al., 1990). The interested reader is referred to a recent review (Roth et al., 2004).

6 Future Directions

The future for research into the roles of VP and OT in brain function is bright. There is ample work to be done in the continuing examination of knockout mice. This work will be considerably aided through the use of conditional knockouts and virally mediated interventions so that the possibility of developmental compensation is avoided. Obviously, the relevance of these studies to human behavior will remain a strong focus. Although not covered in this review, the development of specific and orally active pharmacologic VP and OT agents will play a critical role in sharpening this focus. Recent publications discuss some of the advances in this field of pharmacology (Serradeil-Le Gal et al., 2002; Cirillo et al., 2003; Pitt et al., 2004).

Other recent work in nonhuman animals investigates whether some human diseases might be caused by dysfunctions of the VP and OT systems. Attention has focused on autism and the OTR and V1aR given their roles in social recognition. To date, however, links have been tantalizing but not definitive (Auranen et al., 2002; Kim et al., 2002; Shao et al., 2002; Wassink et al., 2004). The V1aR has also been investigated for roles in sexual fidelity (Cherkas et al., 2004) and eating habits (Bachner-Melman et al., 2004). Although the V1bR has not been implicated in the above behaviors, a recent study has proposed a protective role against major depression (van West et al., 2004). Linkage analysis remains a promising avenue of research. Coupled with the development of better behavioral animal models, the next decade should be a rewarding one for investigators of OT and VP.

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