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Oxytocin: the Great Facilitator of Life

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Abstract

Oxytocin (Oxt) is a nonapeptide hormone best known for its role in lactation and parturition. Since 1906 when its uterine-contracting properties were described until 50 years later when its sequence was elucidated, research focused on its peripheral roles in reproduction. Only over the past several decades have researchers focused on what functions Oxt might have in the brain, the subject of this review.

Immunohistochemical studies revealed that magnocellular neurons of the hypothalamic paraventricular and supraoptic nuclei are the neurons of origin for the Oxt released from the posterior pituitary. Smaller cells in various parts of the brain, as well as release from magnocellular dendrites, provide the Oxt responsible for modulating various behaviors at its only identified receptor.

Although Oxt is implicated in a variety of “non-social” behaviors, such as learning, anxiety, feeding and pain perception, it is Oxt’s roles in various social behaviors that have come to the fore recently. Oxt is important for social memory and attachment, sexual and maternal behavior, and aggression. Recent work implicates Oxt in human bonding and trust as well. Human disorders characterized by aberrant social interactions, such as autism and schizophrenia, may also involve Oxt expression. Many, if not most, of Oxt’s functions, from social interactions (affiliation, aggression) and sexual behavior to eventual parturition, lactation and maternal behavior, may be viewed as specifically facilitating

1. Introduction

Oxytocin (Oxt) is a nonapeptide hormone best known for its role in lactation and parturition. The word “oxytocin” was coined from the Greek words (*ω κ ν ζ, τ ο κ ο ξ ζ*) meaning “quick birth” after its uterine-contracting properties were discovered by Dale (Dale, 1906). Shortly thereafter, the milk ejection property of Oxt was described (Ott and Scott, 1910; Schafer and Mackenzie, 1911). The nine amino acid sequence of Oxt was elucidated in 1953 (du Vigneaud *et al.*, 1953b; Tuppy, 1953) and synthesized soon after (du Vigneaud *et al.*, 1953a; du Vigneaud *et al.*, 1954). Prior to the determination of the structure of the prohormone from the cloned gene for Oxt (Ivell and Richter, 1984), oxytocin was shown to be cleaved from a precursor containing a neurophysin polypeptide during axonal transport to the posterior pituitary (Brownstein *et al.*, 1980). Its sole known receptor (Oxtr) was cloned in 1992 (Kimura *et al.*, 1992). These landmark studies have paved the way for a large body of work, covering not only the roles of Oxt in the periphery, but as we will review, in the central nervous system control of behavior.

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1.1 Structure and evolution of oxytocin

Oxt is composed of nine amino acids (Cys-Tyr-Ile-Gln-Asn-Cys-Pro-Leu-GlyNH₂) with a sulfur bridge between the two cysteines (Fig. 1). The structure of Oxt is very similar to another nonapeptide, vasopressin (Avp), which differs from Oxt by two amino acids. Oxt and Avp are neuropeptides that are evolutionarily well conserved across phyla (Acher *et al.*, 1995; Caldwell and Young, 2006). As a result of gene duplication, the Oxt gene is located on the same chromosome (chromosome 2 in mice and 20 in humans) as Avp but is oriented in opposite transcriptional direction in mammals. Both Oxt and Avp contain three exons and two introns and are highly homologous. The two genes are separated by an intergenic region (IGR) that varies in length across species (e.g., 11 kb in rat and human, and 3.6 kb in mouse). The IGR harbors regulatory DNA sequences within conserved portions for both Oxt and Avp (Gainer *et al.*, 2001; Young and Gainer, 2003, 2009). The preprohormone consists, in order, of the signal peptide, the nanopeptide (Oxt), and the neurophysin (Fig. 1).

1.2 Pharmacology of the oxytocin receptor

Oxytocin is currently known to have only one receptor (Oxtr), unlike Avp which has at least three different subtypes (Caldwell *et al.*, 2008). Oxtr belongs to the rhodopsin-type (class I) G protein-coupled receptor (GPCR) family and is coupled to phospholipase C through G_{αq11} (Gimpl and Fahrenholz, 2001; Young and Gainer, 2003). Much work has gone into creating agonists and antagonists (both peptides and small molecules) with specificity for the Oxtr and little if any activity at the Avp receptors (Manning *et al.*, 2008). Two well known Oxt antagonists are Atosiban (deamino-[D-Tyr²-(O-ethyl)-Thr⁴-Orn⁸]vasotocin) (Akerlund *et al.*, 1985), and OVTA (Elands *et al.*, 1988). Atosiban is clinically used to delay premature delivery (Zingg and Laporte, 2003). However, both antagonists have an affinity for the vasopressin receptor (Avpr) 1a (Akerlund *et al.*, 1999; Manning *et al.*, 1995). Non-peptide Oxtr antagonists such as SSR126768 (Serradeil-Le Gal *et al.*, 2004) and GSK2211149A (McCafferty *et al.*, 2007) have higher specificity and may eventually find clinical use. Synthetic Oxt (known as Pitocin) is used to induce labor and to help milk production (Hayes and Weinstein, 2008). Non-peptide agonists are also under development (Manning *et al.*, 2008). As central Oxt is involved in many behaviors, the use of agonists and antagonists for peripheral indications will need close scrutiny to assess unintended behavioral effects due to passage of the agents through the blood brain barrier. Excellent reviews are available (Gimpl, 2008; Manning *et al.*, 2008).

1.3 Distribution of oxytocin and its receptor in the brain

Oxytocin is primarily synthesized in magnocellular neurons of the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus. The bulk of the peptide is transported to the posterior pituitary where it is released to regulate parturition and lactation. However, some of the Oxt is transported into the dendrites where regulation of its release is critical for controlling the firing patterns of the Oxt neurons (Rossoni *et al.*, 2008). Lesser amounts of Oxt are generated by smaller, parvocellular neurons of the PVN and, depending on species, the bed nucleus of the stria terminalis (BNST), medial preoptic area, and lateral amygdala for release within the brain (Young and Gainer, 2003, 2009).

The distribution of Oxtr expression within the central nervous system (CNS) of numerous species has been examined using *in situ* hybridization histochemistry (Ostrowski, 1998; Yoshimura *et al.*, 1993), a transgenic mouse model (Gould and Zingg, 2003), and receptor autoradiography. A number of species, including rat (De Kloet *et al.*, 1985a; Freund-Mercier *et al.*, 1987; Kremarik *et al.*, 1993; van Leeuwen *et al.*, 1985; Veinante and Freund-Mercier, 1997), mouse (Insel *et al.*, 1991), vole (Insel and Shapiro, 1992), and human (Loup *et al.*, 1991; Loup *et al.*, 1989), have been studied by receptor autoradiography, a technique that indicates where the receptor is transported after synthesis. Sexual and species differences exist in the distributions of the Oxtr, even within the same genus, and these differences are believed

to explain certain variations in behavior (see Section 2). In general, however, Oxt is widely distributed throughout the brain. In rodents, it is often especially prominent in the olfactory bulb (OB) and tubercle, neocortex, endopiriform cortex, hippocampal formation (especially subiculum), central and lateral amygdala, BNST, nucleus accumbens (NAcc), and ventromedial hypothalamus (VMH) (Insel *et al.*, 1991; Veinante and Freund-Mercier, 1997). In humans, expression is prominent in the basal nucleus of Meynert, the nucleus of the vertical limb of the diagonal band of Broca, the ventral part of the lateral septal nucleus, the preoptic/ anterior hypothalamic area, the posterior hypothalamic area, the substantia nigra pars compacta, and the substantia gelatinosa of the caudal spinal trigeminal nucleus and of the dorsal horn of the upper spinal cord, as well as in the medio-dorsal region of the nucleus of the solitary tract (Loup *et al.*, 1991; Loup *et al.*, 1989).

It should be emphasized, as Leng and colleagues discuss (Leng *et al.*, 2008b), that there is not always a match between Oxt immunoreactive terminals and receptor concentrations. Their work shows that dendritic release from magnocellular PVN and SON neurons can influence behavior (Ludwig and Leng, 2006). They suggest, for example, that the lordotic response (see below), shown to rely on VMH Oxt, may reflect action of Oxt that diffused to the VMH from the PVN and SON after dendritic release (Sabatier *et al.*, 2007).

1.4 Sex differences in expression of oxytocin and its receptor

Oxt and OxtR expression is usually higher in females (Carter, 2007; Zingg and Laporte, 2003). The central roles of Oxt on behaviors and physiology are strongly dependent on steroid hormones (discussed below) and gender, and Oxt and OxtR distributions between brains of different sexes have been reported (Carter, 2007; Insel *et al.*, 1991; Tribollet *et al.*, 1997; Tribollet *et al.*, 1992). For example, the numbers of Oxt-immunostained cells and the amounts of Oxt found in females far exceed the numbers and amounts found in males along with greater numbers of oxytocin-immunostained axons (Haussler *et al.*, 1990). In female but not male, rats Oxt binding is increased by high levels of maternal stimulation during infancy, suggesting that epigenetic influence can alter the OxtR expression in a sex-specific manner (Francis *et al.*, 2002). Sexually dimorphic expression of Oxt binding is observed in some brain regions where Oxt is known to have behavioral effects, such as the ventromedial hypothalamic nucleus (VMH), while other areas such as the central nucleus of the amygdala, do not show sexual dimorphism (Uhl-Bronner *et al.*, 2005).

1.5 Control of oxytocin and oxytocin receptor by steroid hormones

Estrogen receptor (ER) β is present in magnocellular neurons of the PVN and SON (Forsling *et al.*, 2003; Hrabovszky *et al.*, 2004). The ER β mRNA expression there is negatively regulated by basal glucocorticoid secretion and by hyperosmotic stimulation (Somponpun *et al.*, 2004). The rat and human Oxt gene promoters contain estrogen-response elements (ERE) and are stimulated by estrogen (E) and thyroid hormones (Mohr and Schmitz, 1991; Richard and Zingg, 1990). A recent *in vivo* study suggests that E action on the Oxt gene is more likely to involve a DNA-independent mechanism than direct regulation by ERs (Stedronsky *et al.*, 2002). Interestingly, the poly(A) tail, which is important for mRNA stability, is increased by osmotic stimulation (Carter and Murphy, 1989) and blocked by gonadectomy (Crowley and Amico, 1993).

It is well known that E stimulates expression of OxtR in the uterus (see (Richter *et al.*, 2004) and references therein) and greatly increases the expression in the kidney (Breton *et al.*, 1996; Ostrowski *et al.*, 1995). OxtR expression increases in the myoepithelial cells of the breast during pregnancy and lactation (Soloff, 1982). In rats, OxtR binding and mRNA levels in the brain are increased with E and testosterone treatment and decreased by castration (Breton and Zingg, 1997; Larcher *et al.*, 1995; Stevenson *et al.*, 1994; Tribollet *et al.*, 1990). However, this

effect may depend on the species studied (Insel *et al.*, 1993). Oxt expression also increases in a number of brain areas just prior to parturition (Meddle *et al.*, 2007), accompanied by a concomitant increase in gonadal hormones, particularly E (Rosenblatt *et al.*, 1988).

The VMH is an important nucleus for the regulation of sex behavior and the role of Oxt within the VMH has been the focus of intense study. Within the VMH of males and females, Oxt is particularly sensitive to gonadal steroids (Bale and Dorsa, 1995; Bale *et al.*, 1995; Coirini *et al.*, 1989; De Kloet *et al.*, 1986; De Kloet *et al.*, 1985b; Johnson *et al.*, 1991; Quinones-Jenab *et al.*, 1997).

There are complete palindromic EREs in the promoters of the Oxt genes of mice and rats (Bale and Dorsa, 1997; Kubota *et al.*, 1996), as well as half-palindromic EREs in those of mice, rats and humans (Inoue *et al.*, 1994; Kubota *et al.*, 1996; Rozen *et al.*, 1995). It is likely that E can act on the half palindromic EREs, albeit with lower affinity (Sanchez *et al.*, 2002). A recent study suggests that a membrane bound receptor for E may also regulate expression within the PVN and SON (Sakamoto *et al.*, 2007). The Oxt 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 (Bale and Dorsa, 1998; Gimpl and Fahrenholz, 2001; Rozen *et al.*, 1995). E-induced Oxt binding in the brain is abolished in ER- α knockout (KO) mice, whereas the basal Oxt expression in the brain of the KO mice is similar to controls (Young *et al.*, 1998).

1.6 Gene inactivation in mice

A large number of studies have utilized KO mouse models. Oxt KO mice were first introduced in 1996 by two groups (Nishimori *et al.*, 1996; Young *et al.*, 1996b). Oxt KO mice display normal parturition even though female KO do not show milk ejection (Nishimori *et al.*, 1996; Young *et al.*, 1996b). These two groups later independently generated Oxt KO mice (Lee *et al.*, 2008; Takayanagi *et al.*, 2005) with one line showing late-onset obesity (Takayanagi *et al.*, 2008). The other line is a conditional KO that allows temporal and spatial Oxt elimination (Lee *et al.*, 2008). Detailed descriptions of the behavioral deficits in these Oxt and Oxt KO mice are presented in Section 2.

Other eliminated genes have significant effects on Oxt expression or effectiveness. For example, absence of the basic helix-loop-helix-PAS *Sim1* (Michaud *et al.*, 1998) or the POU protein *Brn-2* (Nakai *et al.*, 1995; Schonemann *et al.*, 1995) genes lead to elimination of magnocellular neurons of the PVN and SON. As absence of *Sim1* also leads to lack of *Brn-2*, it would seem that *Sim1* functions upstream of *Brn-2* (Michaud *et al.*, 1998). Knockout mice lacking CD38, a protein that aids in release of Oxt show decreased release of Oxt accompanied by defects in maternal and social behaviors (Jin *et al.*, 2007).

2. Behavior

Oxt is involved in the regulation of a wide variety of behaviors; many times, these behaviors are intertwined (e.g., more social species tend to have monogamous relationships and to be biparental). To better elucidate the role Oxt has in each of these behaviors, we have separated this review into two broad categories: social behaviors and non-social behaviors. Within each category we will separately discuss various behaviors affected by Oxt, with a concerted effort to draw out the similarities between them. An additional section has been added at the end discussing the role Oxt has in various behaviors that do not readily fit under either of the two aforementioned categories. Also, it should be noted that while Oxt is often discussed in concert with Avp, the main focus of this review is Oxt, so mention of the role of Avp on these same behaviors will be limited. For recent Avp reviews, see ((Caldwell *et al.*, 2008); (Raggenbass, 2008); (Lim and Young, 2006); and (Landgraf, 2005)).

2.1 Social Behavior

The ability to recognize a conspecific is imperative in determining the proper response to that individual, and formation of a 'social memory' of individuals is vital for display of appropriate behaviors within a social group. For inter-sex interactions, the appropriate behaviors are often affiliative in nature, which allows for reproduction, pair-bonding, and parental behaviors. For same-sex interactions, particularly male-male interactions, the appropriate behaviors are often aggressive in nature and center around competition for mates and other resources. Across species, Oxt is important in regulating the formation of social memories, as well as displays of affiliative and aggressive behaviors. The next three sections will delve into the particular roles that Oxt has in regulating social behaviors (social recognition; affiliation; aggression); these sections are summarized in Table 1. For recent reviews of Oxt effects on social behaviors, see (Neumann, 2008; Neumann and Landgraf, 2008).

2.1.1. Social memory and social recognition—Recognition of individuals is important for everyday life. Without the ability to determine friend from foe, it is difficult to display the appropriate behaviors (either affiliative or aggressive, respectively). The formation of a social memory of individuals is therefore vital, and in rodents relies primarily on volatile and pheromonal olfactory cues. This differs from primates, which rely primarily on both visual and auditory cues. In rodents, Oxt influences social memories by affecting the processing of these olfactory cues (for a recent review, see Sanchez-Andrade and Kendrick, 2008).

Social memory is commonly examined in rodents through three paradigms: habituation-dishabituation, social recognition, and social discrimination. In the first, a subject animal is exposed to the same "stimulus" animal over repeated trials, and decreases investigation through habituation. Following habituation, a novel animal is presented, which typically results in an increase in investigation time, or dishabituation (Winslow and Camacho, 1995). In the social recognition paradigm, a subject animal is exposed to a stimulus animal and after a predetermined period of time is either re-exposed to the same stimulus animal or to a novel stimulus animal. Typically, the subject spends a greater amount of time investigating the novel animal (Dantzer *et al.*, 1987). The third paradigm, social discrimination, is similar to social recognition, except that on the re-exposure trial both the same and novel stimulus animals are presented simultaneously, forcing the subject animal to choose between the two (Engelmann *et al.*, 1995). For detailed protocols, see (Winslow, 2003).

Choleris and coworkers have suggested a gene micronet involving the four genes coding ER α , ER β , Oxt and Oxt r as the regulatory basis of social recognition in the brain (Choleris *et al.*, 2004). The interactions between the E and Oxt systems are quite intricate. For example, neonatal manipulations of Oxt r stimulation lead to changes in brain ER and Oxt levels in both juveniles and adults (Cushing *et al.*, 2003; Kramer *et al.*, 2007). Even this proposed micronet can only be part of the basis of social recognition, as it is known that other substances (e.g., vasopressin (Bielsky *et al.*, 2004; Wersinger *et al.*, 2002)) are necessary.

2.1.1.1. Social memory/recognition in males: In males, a great body of evidence indicates that both neuropeptides Avp and Oxt influence social memory. The role of Avp in social memory/recognition has been described previously (Caldwell *et al.*, 2008); this review will focus on the role of Oxt in social memory/recognition. Early work by Dluzen and colleagues indicates that Oxt likely influences social recognition responses in males by affecting the ability to process odors. Infusion of Oxt into the OB facilitates social recognition at both a 30-min and 120-min delay compared to vehicle-treated animals, but infusion of the Oxt antagonist desGly-NH₂,d(CH₂)₅[Try(Me)²,Thr⁴,Orn⁸]vasotocin (AOVT) into the same region of the OB fails to block social recognition at either time delay (Dluzen *et al.*, 1998a). Retrodialysis of Oxt into the OB increases norepinephrine (NE) release (Dluzen *et al.*, 2000). Infusion of 6-

hydroxydopamine, which destroys NE terminals, directly into the OB results in a complete lack of social recognition, even with co-infusion of Oxt (Dluzen *et al.*, 1998b). Specifically, the actions of NE on the α -adrenoceptors in the OB are necessary, as infusion of clonidine (an alpha-adrenoceptor agonist) preserves social recognition, while phentolamine (an alpha-adrenoceptor antagonist) prevents social recognition, even in the presence of Oxt (Dluzen *et al.*, 2000).

Oxt also facilitates social recognition when administered in other regions. Infusion into the lateral ventricles significantly enhances social recognition 120 minutes later at doses of 1fg – 10 ng/rat when injected after the first encounter (Benelli *et al.*, 1995), indicating a role for Oxt in the acquisition phase of social memory (see (Ferguson *et al.*, 2002) for review). Similarly, infusion of the Oxt antagonist d(CH₂)₅[Tyr(Me)²-Orn⁸]vasotocin (CPOVT) 5 minutes before Oxt injection abolishes the memory-enhancing effect (Benelli *et al.*, 1995). Social recognition is facilitated by Oxt injection into the medial preoptic area of the hypothalamus (mPOA) with a wide range of doses (0.3–1000pg), but not when injected into the septum (Popik and van Ree, 1991). Interestingly, Avp facilitates social recognition when injected into the septum (Engelmann and Landgraf, 1994), but not the mPOA (Popik and van Ree, 1991); see (Caldwell *et al.*, 2008) for review), indicating that these two neuropeptides influence social recognition in different brain regions. Finally, subcutaneous administration of Oxt and related peptides containing the C-terminal glycylamide (i.e., Oxt-(1–9), Oxt-(7–9), and Oxt-(8–9)) have been shown to facilitate social recognition at low doses (Popik *et al.*, 1996). Access to the CNS by this route of administration is problematical, as is the site of action.

The development of Oxt and Oxt receptor KO mice has led to the further characterization of Oxt's role in social recognition responses. Male Oxt KO mice fail to develop social memory on both the habituation-dishabituation test (Ferguson *et al.*, 2000; Lee *et al.*, 2008) and the social recognition test (Ferguson *et al.*, 2001). Oxt in the medial amygdala is necessary to facilitate social recognition, as demonstrated by c-fos activation in the medial amygdala of wildtype (WT) but not Oxt KO mice during the initial exposure (Ferguson *et al.*, 2001). Interestingly, two independently derived lines of Oxt KO mice fail to show any deficits in general sociability (as measured by the social approach task; (Crawley *et al.*, 2007), indicating that Oxt is primarily involved in the memory component of social recognition (see Section 2.2.1 for the role Oxt plays in learning and memory).

Recently, a similar impairment in social recognition in two lines of OxtR KO mice was described. Specifically, unlike WT controls, OxtR KO mice continue to investigate a 'familiar' female as if she were 'novel' (Takayanagi *et al.*, 2005). Furthermore, we generated a line of conditional OxtR KO mice to reduce OxtR expression in parts of the forebrain (OxtR^{FB/FB}). Compared to WT littermate controls, OxtR^{FB/FB} mice also have a social recognition impairment but in a different manner, with decreased investigation of both 'familiar' and 'novel' females on the second trial, but at intermediate levels (Figure 3) (Lee *et al.*, 2008). As OxtR^{FB/FB} mice can distinguish between familiar and novel stimulus females on the habituation-dishabituation task, it is unlikely that the decreased investigation is due to a loss of interest in the social recognition tasks. Why the OxtR KO and OxtR^{FB/FB} mice should differ in social recognition performance is unclear, and is currently being investigated.

Generation of KO mice has allowed for investigation into the importance of proteins that regulate Oxt secretion. Oxt release is controlled, in part, by intracellular calcium (Ca²⁺) stores (reviewed in Ludwig and Leng, 2006). CD38 is a transmembrane glycoprotein that, through formation of cyclic ADP-ribose and nicotinic acid adenine dinucleotide phosphate, mobilizes Ca²⁺ and affects Oxt secretion. CD38 KO mice show normal synthesis and storage of Oxt in axon terminals, but abnormally low plasma and high hypothalamic Oxt concentrations, indicating abnormal release of Oxt in these mice, from both axon terminals and soma and/or

dendrites (Jin *et al.*, 2007). Interestingly, these mice show deficits in social recognition similar to those of the Oxt and Oxt^{-/-} mice described above.

2.1.1.2. Social memory/recognition in females: Social recognition differs between males and females. Females investigate stimulus animals less than males (Bluthe and Dantzer, 1990), but seem to retain the social memory for longer durations than males (Bluthe and Dantzer, 1990; Engelmann *et al.*, 1998). Intracerebroventricular administration of the oxytocin antagonist AOVY abolishes social recognition in females, whereas the Avpr1a receptor antagonist d(CH₂)₅Tyr(Me)²AVP does not (Engelmann *et al.*, 1998).

Similar to male social recognition, the medial amygdala modulates female social recognition. Antisense oligonucleotides specific for the Oxt administered i.c.v. into the medial amygdala several days prior to testing significantly reduce social recognition in females, indicating that Oxt expression in that region is necessary for proper social recognition (Choleris *et al.*, 2007). Additionally, social recognition is mediated by neuropeptide - steroid hormone interactions. In males, testosterone regulates the effects of neuropeptides, particularly Avp (Bluthe *et al.*, 1990), on social recognition; in females, E appears to regulate Oxt effects on social recognition. Specifically, ER α , ER β , and Oxt KO mice all have very similar deficits in social recognition on the habituation-dishabituation test, with all three KO lines failing to habituate to a 'familiar' animal or dishabituate with a 'novel' animal (Choleris *et al.*, 2003). Similarly, in a social discrimination task, the three lines show either complete impairment (Oxt and ER- α KO mice) or partial impairment (ER β KO mice), indicating that all three genes are necessary to some degree for social recognition in females (Choleris *et al.*, 2006). Lastly, Oxt facilitates long-term potentiation in mitral cells of the accessory OB (Fang *et al.*, 2008). Oxt release in the OB modulates social recognition, with vaginocervical stimulation during proestrus/estrus (high E levels) significantly increasing release of Oxt in the OB, thereby enhancing social recognition 5 hours after first exposure (Larrazolo-Lopez *et al.*, 2008).

Another olfactory-based social memory in females is the Bruce effect, where housing a female with an unfamiliar male blocks pregnancy (Bruce, 1959) due to the chemosensory signals present in the new male's urine (Brennan, 2003; Dominic, 1966). Oxt KO, heterozygote (HET), and WT females display pregnancy block in response to an unfamiliar male, as expected; only Oxt KO females block pregnancy when a familiar male (their previous mate) is encountered, indicating a social memory deficit (Wersinger *et al.*, 2008). Interestingly, continuously paired Oxt KO females do not pregnancy block, likely because with constant exposure, they do not have the opportunity to 'forget' their mates. Avpr1b plays a role in the Bruce effect as well, but in a different manner, as Avpr1b KO females do not exhibit pregnancy block with an unfamiliar male (Wersinger *et al.*, 2008).

2.1.1.3. Human studies: Recently, researchers have begun to examine Oxt effects on human social recognition, primarily by testing recognition of faces. Generally, Oxt seems to enhance memory for faces; whether or not the emotion displayed on the faces is relevant remains unclear. Oxt administered intranasally to males and females after viewing male faces (with happy, angry, or neutral expressions) significantly improves recognition memory 30 minutes and 24 hours later for neutral and angry faces only (Savaskan *et al.*, 2008). Similarly, intranasal Oxt increases memory for angry faces in both males and females without influencing response time, accuracy, or gaze time (Guastella *et al.*, 2009), indicating that Oxt may influence face recognition at very early stages of perceptual processing. In contrast, an earlier study by the same group reports that Oxt (administered to males only) increases memory for previously seen faces with happy expressions only, not angry or neutral (Guastella *et al.*, 2008c). Why this discrepancy exists remains unclear, but may be due to presentation of different stimulus faces (male: (Savaskan *et al.*, 2008); male and female: (Guastella *et al.*, 2008c); drawings: (Guastella *et al.*, 2009)). Perhaps significantly, the former study gave Oxt after the acquisition

phase while it was given prior to the acquisition phase in the latter two. In a more recent study, intranasal Oxt was given to male subjects 40 minutes prior to presentation of faces. Twenty-four hours later, subjects treated with Oxt had better memory for faces seen the previous day, with no influence on memory for previously seen non-social stimuli (Rimmele *et al.*, 2009). This is a further indication that Oxt is specifically involved in memory of social stimuli.

As discussed above (Sections 2.1.1.1 and 2.1.1.2), Oxt in the medial amygdala underlies social recognition in rodents. Similarly, the human amygdala seems important for facial recognition in humans. Lower blood oxygenation level dependent functional magnetic resonance imaging (fMRI) activity is seen in the right amygdala after intranasal Oxt, as compared with placebo, when viewing emotional (happy, fearful, or angry expressions) faces, regardless of type of emotion displayed (Domes *et al.*, 2007a). Similarly, male subjects have reduced amygdala activation when shown angry or fearful expressions following Oxt administration (Kirsch *et al.*, 2005). The same reduction is not seen when presented with non-social stimuli, such as fearful or threatening scenes. Furthermore, functional amygdala connections to upper brainstem regions (such as the periaqueductal gray) are significantly reduced with intranasal Oxt (Kirsch *et al.*, 2005), indicating that Oxt can affect a circuit for social recognition and response. However, it should be remembered that although intranasal application of large proteins may reach the olfactory bulbs (Balin *et al.*, 1986) and small peptides the CSF (Born *et al.*, 2002), no studies have shown that the intranasal Oxt is reaching the CNS areas involved in facial recognition.

2.1.1.4. Conclusion: Administration of Oxt agonists and antagonists, as well as studies using Oxt and Oxt^r KO mice, indicate a positive relationship between Oxt and social memory in both males and females. Data from clinical studies reveal similar results, with Oxt promoting face recognition in humans. In both non-humans and humans, the amygdala seems important for recognition of social stimuli. Further investigation of social memory using techniques such as conditional knockouts (Lee *et al.*, 2008) and site-specific lentivirus injections will allow more detailed analyses of the role of Oxt and the Oxt^r in social memory. Earlier reviews have also been written detailing Oxt and Avp effects on social memory and recognition (Ferguson *et al.*, 2002); (Winslow and Insel, 2004); and (Bielsky and Young, 2004).

2.1.2. Affiliation—Affiliation, or social bonding between individuals, is one of the most highly motivated social behaviors, as forming social bonds can counteract the stress and anxiety provoked by social isolation in rodents (Grippe *et al.*, 2007). Affiliative behaviors are highly species-specific (for review see (Carter, 1998). In rodents, the most readily quantifiable affiliative behaviors are sexual behavior, pair bonding, and parental care. The regulation of these behaviors by Oxt will be discussed in this section (for review of Avp regulation of affiliative behaviors see (Caldwell *et al.*, 2008)).

Approximately 3% of all mammals display monogamous sexual relationships (Kleiman, 1977). Monogamy consists of a set of distinguishing characteristics including (1) sharing of nest and territory by a breeding pair during breeding and non-breeding seasons; (2) aggressive displays by both sexes towards unfamiliar conspecifics; (3) bi-parental care; (4) socially regulated reproduction; and (5) incest avoidance via suppression of puberty in the natal group (Carter *et al.*, 1995; Insel and Fernald, 2004). Pair bond formation has been largely studied in voles, as both monogamous (prairie and pine voles) and non-monogamous (montane and meadow voles) species exist, with corresponding differences in Oxt^r binding across monogamous and non-monogamous species (Winslow *et al.*, 1993b). Comparisons between these species allows for quantification of the development of social bonds, such as pair bonding (see (Young *et al.*, 2008) for review).

In the laboratory, pair bonding is measured with the partner preference task, in which animals are given a choice between spending time with a familiar, mated partner and a novel “stranger” animal. Partner preference is operationally defined as an animal spending twice as much time with the familiar partner compared to the novel ‘stranger’. Monogamous male voles readily make this distinction, and spend less than 20% of their time alone, compared with polygynous voles, which remain alone about 90% of the time (Carter *et al.*, 1995).

Oxt facilitates pair bonding in monogamous female voles, likely due to its release during mating (see Section 2.1.3; but mating is not always required for partner preference: see (Williams *et al.*, 1992). Partner preference in females seems to be exclusively under Oxt control, as infusion of Avp or Avp antagonist fails to affect partner preference in female prairie voles (Insel and Hulihan, 1995; Insel *et al.*, 1998), and pretreatment with an Oxtr antagonist prevents partner preference (Cho *et al.*, 1999; Cushing and Carter, 2000). Furthermore, i.c.v. or s.c. Oxt infusion (over 24 hrs) into female prairie voles facilitates formation of pair bonds, while treatment with an Oxtr antagonist prior to mating prevents pair bonding (Williams *et al.*, 1994). The ability of Oxt-treated females to develop a partner preference is dose dependent, with high doses (above 2 mg/kg) decreasing partner preference (Bales *et al.*, 2007b). Oxt may interact with E to facilitate pair bonding, as administration of the endocrine disrupting chemical methoxychlor (MEX) to female pine voles significantly reduces Oxt binding in the cingulate cortex and time spent engaged in social activity (Engell *et al.*, 2006).

Oxt’s role in male partner preference is less clear. Acute Oxt treatment (just prior to testing) has been shown to facilitate partner preference in males (Cho *et al.*, 1999). Furthermore, developmental exposure to Oxt (1 injection administered on postnatal day 1 (PND 1)) does result in formation of partner preference in male prairie voles as adults (Bales and Carter, 2003a). However, other studies indicate no role for Oxt in male partner preference (Winslow *et al.*, 1993a); Cushing & Carter, 2000), or an interactive regulation of pair bonding by both Oxt and Avp (Cho *et al.*, 1999; Liu *et al.*, 2001). Recent data indicates that the latter is likely, as Oxt seems to alter expression of Avpr1a (Bales *et al.*, 2007). Cross-communication between the two systems could regulate pair bonding in males.

The sexually dimorphic effects of Oxt on pair bonding may be due to differences in Oxt and Avp pathways and receptor distributions throughout the vole brain. The female brain is generally more susceptible to effects of Oxt. Administration of Oxt on PND1 alters aggression in female prairie voles, but not males (Bales and Carter, 2003b). Treatment with Oxt and the Oxtr antagonist CPOVT on PND1 results in increased Oxt immunoreactive (Oxt-ir) neurons in females, but not males (Yamamoto *et al.*, 2004). Recently, the same Oxt antagonist was shown to increase c-fos activity in the central amygdala of females when mated, which could affect later social behavior (Kramer *et al.*, 2006).

Interestingly, distribution of OT neurons is not gender-specific in either monogamous or non-monogamous voles (Wang *et al.*, 1996). The prairie vole does have fewer Oxt-ir neurons in the mPOA and BNST when compared to the montane vole, however (Insel *et al.*, 1995). Furthermore, distribution patterns and quantity of Oxtr differ between monogamous and polygamous voles (Insel and Shapiro, 1992). Generally, monogamous prairie voles have greater Oxtr in the frontal cortex, NAcc, BNST, amygdala, and thalamus, while Oxtr in the polygamous montane vole is concentrated in lateral septum and VMH (Insel and Shapiro, 1992). While both Oxtr and Avpr1a in the ventral forebrain seem important in regulating pair bonding and partner preference (Insel and Shapiro, 1992; Insel *et al.*, 1994), the two receptors have different expression patterns in prairie voles, with Oxtr specifically relegated to the shell and core of the NAcc in prairie voles (Lim *et al.*, 2004), where Oxt-dopamine interactions aid in partner preference formation in female prairie voles (Liu and Wang, 2003). In contrast, non-monogamous voles, rats and mice have very low levels of Oxtr binding in the NAcc (Olazabal

and Young, 2006b). Administration of adeno-associated viral vector encoding the vole Oxt gene into the NAcc of monogamous prairie voles results in accelerated formation of partner preference in comparison to untreated prairie voles (Ross *et al.*, 2009). However, the same virus administered into the NAcc of polygamous meadow voles does not facilitate partner preference, indicating that some other mechanism likely underlies partner preference in polygamous species (Ross *et al.*, 2009). The *Oxtr* genes of monogamous and non-monogamous species have highly homologous coding and near promoter regions, so that differences in more distant regulatory elements or levels of their cognate binding proteins may explain the expression differences (Young *et al.*, 1996a).

Due to the ability to perform comparative studies across different vole species, *Microtus* voles are the most heavily studied in terms of pair bonding and partner preference (Young *et al.*, 2008). Despite the difficulties in studying ‘partner preference’ in other mammalian species, Oxt has been shown to affect sociability. Intracranial and subcutaneous Oxt injections increase the amount of social contact in male rats (Witt *et al.*, 1992), female mongolian gerbils (Razzoli *et al.*, 2003), and male squirrel monkeys (Winslow and Insel, 1991). Oxt increases flank marking (Harmon *et al.*, 2002b) and decreases aggression (Harmon *et al.*, 2002a) in female Syrian hamsters. The social and non-social species of tuco-tuco (genus *Ctenomys*), a South American rodent, differ highly in Oxt binding throughout the brain, although not in the same manner as microtine rodents (Beery *et al.*, 2008). Bonnet macaques, which have a more affiliative social structure than the closely related pigtail macaques, have higher levels of Oxt in CSF than do pigtails (Rosenblum *et al.*, 2002).

2.1.2.3. Parental Behavior: 2.1.2.3.1. Maternal Care: During pregnancy and when nursing pups, both Oxt and the Oxtr are altered in the female rat brain, particularly the ventral septum (Landgraf *et al.*, 1991), SON (Caldwell *et al.*, 1987; Landgraf *et al.*, 1992; Mezey and Kiss, 1991), PVN (Caldwell *et al.*, 1987), and, perhaps, within the dorsal hippocampus (Landgraf *et al.*, 1992). Similar increases in Oxt expression are seen in the PVN and SON of postpartum female prairie and montane voles (Wang *et al.*, 2000), in the PVN, SON, and lateral hypothalamic area on postpartum day 1 in rabbits (Caba *et al.*, 1996), and in the OB of primiparous and multiparous ewes at parturition (Levy *et al.*, 1995).

Oxt expression is also significantly increased at parturition throughout the brain (particularly in the SON, mPOA, BNST, OB, and amygdala), with Oxtr expression returning to the levels seen in virgin rats by 12 hours postpartum (Meddle *et al.*, 2007). Similarly, female prairie and montane voles have significantly greater Oxtr binding in the VMH than virgin females or males, although the expression patterns differ between the two species (Wang *et al.*, 2000). Interestingly, specific Oxtr binding sites have not been found in the OB of postpartum ewes (Levy *et al.*, 1992), despite an increase in Oxt levels in the same region (Levy *et al.*, 1995).

A likely reason for increased expression of Oxt and the Oxtr is to facilitate the onset and maintenance of maternal behavior, which is strongly regulated by Oxt (see (Leng *et al.*, 2008a) for a recent review). Injections of Oxt i.c.v. to gonadally-intact females significantly increases the display of “full maternal behavior” (display all of the following: grouping pups, licking pups, crouching over pups, nest building, and pup retrieval), but only with high endogenous E levels (Pedersen and Prange, 1979). In OVX females, Oxt is only able to induce maternal behavior in females primed with estradiol benzoate (EB) (Pedersen and Prange, 1979). Furthermore, Oxt effects on maternal behavior are dose-dependent, with higher doses eliciting higher maternal behavior responses in EB-primed rats (Pedersen *et al.*, 1982). Oxt may specifically alter grooming and posturing over pups, as i.c.v. infusion of the selective Oxt antagonist OVTA significantly increases self-grooming and frequency of lying prone on pups instead of facilitating nursing by remaining elevated and upright (Pedersen and Boccia, 2003). Oxt seems to interact with the dopamine and serotonin systems to control certain aspects

of maternal behavior, including grooming (Johns *et al.*, 2005). Oxt induces full maternal behavior more readily than Avp, and maintains full maternal behavior for up to 6 hours after administration (Pedersen *et al.*, 1982). Similarly, in OVX females primed with E and progesterone (P), anti-Oxt antiserum i.c.v. significantly reduces maternal behavior after 2, 6, and 25 hours compared to animals receiving anti-vasopressin antiserum or normal rabbit serum (Pedersen *et al.*, 1985). A recent review detailing the role of E and ERs on maternal care carefully describes the interactions between E and Oxt in facilitating maternal behavior (Cameron *et al.*, 2008).

In many species, including rats, natural variations in maternal behavior are seen. Some dams show high levels of pup licking and grooming and arched-back nursing (High LG-ABN), while others show low levels of these behaviors (Low LG-ABN); High LG-ABN mothers have higher levels of Oxtr than Low LG-ABN mothers in a number of regions known to underlie maternal behavior (i.e., the BNST, mPOA, and lateral septum) and maternal aggression (i.e., the central nucleus of the amygdala; Champagne *et al.*, 2001; Francis *et al.*, 2000). I.c.v. injections of the Oxtr antagonist OVTA effectively turns High LG-ABN mothers into Low LG-ABN mothers (Champagne *et al.*, 2001), further indicating that activation of Oxtr in the brain is required for proper display of maternal behavior. E is again shown to play a role as s.c. administration significantly increases Oxtr binding in the mPOA and lateral septum of High, but not Low, LG-ABN mothers (Champagne *et al.*, 2001). Individual variations in maternal behavior are transmitted across generations, with female offspring (biological or cross-fostered) of High LG-ABN mothers growing up to be High LG-ABN mothers themselves (Francis *et al.*, 1999). Interestingly, Oxtr binding in the central nucleus of the amygdala and BNST is higher in female offspring of High LG-ABN mothers (Francis *et al.*, 2002).

Rodent species differ in expression of alloparental behavior (caring for non-related pups). In a highly social rodent species, the naked mole rat, only the queen gives birth and nurses pups, but many individuals participate in caring for pups. Interestingly, high levels of Oxt immunoreactive fibers are found in the NAcc and mPOA (Rosen *et al.*, 2008), areas that are implicated in maternal care. Juvenile and adult prairie voles readily express 'spontaneous' maternal behavior (Olazabal and Young, 2005), juvenile rats require pup exposure (Mayer and Rosenblatt, 1979), and juvenile mice failing to show any spontaneous maternal behavior (Gandelman, 1973). The Oxtr may underlie species differences in spontaneous maternal behavior, as Oxtr density is highest in the NAcc of juvenile prairie voles, intermediate in juvenile rats, and lowest in juvenile mice and meadow voles (Olazabal and Young, 2006b). The exact opposite pattern of Oxtr expression is seen in the lateral septum, with Oxtr binding lowest in juvenile prairie voles and rats (Olazabal and Young, 2006b). A follow-up study with sexually-naïve adult female prairie voles shows that maternal behavior display and Oxtr binding in the NAcc are positively correlated; injection of the Oxtr antagonist OVTA into the NAcc completely abolishes maternal behavior (Olazabal and Young, 2006a). However, elevation of Oxtr through adeno-associated virus delivery in female prairie voles does not increase further alloparental behavior (Ross, *et al.*, 2009).

The recent development of Oxt and Oxtr KO mice permits further examination of the role of Oxt and the Oxtr in maternal behaviors. Two separate lines of Oxt KO mice have been developed; in both lines, females fail to successfully eject milk but display maternal behavior identical to WT mice (Nishimori *et al.*, 1996; Young *et al.*, 1996b). However, a recent detailed study of maternal behavior by Oxt KO and WT nulliparous females towards foster pups indicates that fewer Oxt KO females retrieve pups; those that do retrieve pups retrieve fewer pups, and Oxt KO females groom themselves and pups less than WT females (Pedersen *et al.*, 2006). Similar deficits are seen in both Oxtr KO virgin postpartum females (Takayanagi *et al.*, 2005).

2.1.2.3.2 Paternal Care: Much less is known about the role of Oxt in paternal behavior, likely due to the small number of species in which males care for young. However, certain species of rodents (prairie voles and California mice, *Peromyscus californicus*) are biparental, providing a model with which to examine a possible role for Oxt in paternal care. In male California mice, plasma Oxt levels are significantly higher in expectant fathers from days 1–15 of pregnancy, compared to virgin males or non-expectant fathers (Gubernick *et al.*, 1995), indicating that Oxt may prepare monogamous males for display of paternal behavior. However, postpartum Oxt levels do not differ between paternal and non-paternal males, and Oxt levels are elevated in males removed from their partner and pups (Gubernick *et al.*, 1995).

I.c.v. Oxt does not increase alloparental behavior in reproductively-naïve male prairie voles (Bales *et al.*, 2004). Furthermore, only combined treatment with Oxt and Avp antagonists reduces alloparental behavior, not treatment with either antagonist alone (Bales *et al.*, 2004), suggesting that either the Oxt or Avp system may be sufficient for alloparental behavior. However, administration of the Oxt antagonist CPOVT on postnatal day 1 results in significantly reduced alloparental care by males when 21 days old (Bales *et al.*, 2004). Neonatal exposure to Oxt or an Oxt antagonist may affect later paternal care, but there is little evidence that Oxt during adulthood is responsible for paternal care in the same manner as has been shown for maternal care. Instead, Oxt may indirectly promote paternal care by promoting release of prolactin (Liu and Ben-Jonathan, 1994) that is more directly implicated in paternal care in rodents (Wynne-Edwards and Timonin, 2007) and primates (Ziegler, 2000).

Interestingly, changes in Oxt binding are seen in non-monogamous male voles as well. Sexually and parentally experienced male meadow voles have greater Oxt binding compared to inexperienced males in the accessory olfactory nucleus, BNST, lateral septum, and lateral amygdala (Parker *et al.*, 2001). Whether these changes in Oxt underlie paternal behavior has yet to be assessed, as non-monogamous species such as the meadow vole do not readily display alloparental behavior.

2.1.2.4. Conclusion: Oxt is greatly implicated in the formation of affiliative bonds for both partners and pups, although in the latter case there is greater evidence that Oxt primarily acts in females. Generally, Oxt release due to vagino-cervical stimulation during mating aids in sexual receptivity, the formation of affiliative bonds, and later display of maternal behavior. For detailed reviews on Oxt and social bonding, see (Carter, 2003; Carter *et al.*, 1995; Insel, 1997; Insel and Fernald, 2004; Insel *et al.*, 1998; Lim and Young, 2006). For a recent detailed review on the contribution of Avp and both Avpr receptor subtypes to social bonding see Caldwell *et al.* (Caldwell *et al.*, 2008). As discussed next, Oxt is also important for male and female sexual behavior.

2.1.3. Sexual behavior—One of the earliest discovered functions of Oxt was the facilitation of smooth muscle contractions in the uterus during labor (Sheldrick and Flint, 1985). Since then, Oxt has been found to regulate maternal behavior (see Section 2.1.2.3.1) and to aid in forming social bonds as adults (see Section 2.1.2). Additionally, Oxt plays a key role in regulating sexual behaviors in both male and female rodents. In male rodents, Oxt is implicated in erectile functioning, copulatory activity, and ejaculation (reviewed in Witt, 1995). In female rodents, Oxt activity is most studied in voles, rats, and rabbits. In female rats, in particular, regulation of copulatory behavior occurs through interactions between E and Oxt (reviewed in Witt, 1995). The following sections discuss how Oxt influences behaviors relating to sexual activities in both male and female rodents, as well as humans.

2.1.3.1. Sex behavior in males: Acute administration of Oxt enhances male sexual behavior, while intravenous Oxt injections accelerate time to ejaculation and number of ejaculations in rabbits (Melin and Kihlstrom, 1963) and the number of intromissions prior to ejaculation in

rats, although only at low doses (Stoneham *et al.*, 1985). Similarly, both i.c.v. and i.p. Oxt injections accelerate time to ejaculation and decrease time between mating attempts in rats (Arletti *et al.*, 1985). Oxt facilitates erections in an inverted U-shaped manner, with high doses inhibiting erection frequency (Argiolas *et al.*, 1987) as well as decreasing mounting bouts and increasing intromission latencies in male rats (Stoneham *et al.*, 1985).

One hypothesis is that Oxt, at high levels, contributes to feelings of sexual satiety and therefore inhibits male sexual behavior. During mating bouts with a receptive female, Oxt is released within the PVN of male rats and is accompanied by reduced anxiety-like behavior up to 30 minutes after mating (Waldherr and Neumann, 2007). The release of Oxt during mating could contribute to sexual satiety. Indeed, acute i.c.v. Oxt can inhibit sexual behavior in male prairie voles (Mahalati *et al.*, 1991). Unlike acute administration, chronic i.c.v. Oxt infusion has no long-term effects on number of mounts, intromissions, or ejaculations in male rats (Witt *et al.*, 1992), perhaps due to decreased Oxt receptor density throughout the brain (Insel *et al.*, 1992). However, chronic Oxt infusion does increase interaction time with the female without increasing sexual behavior (Witt *et al.*, 1992), further implicating Oxt in sexual satiety (for review see (Carter, 1992) and general male social behavior (see Section 2.1.1.1).

Oxt does not act alone to bring about penile erections. Oxt is unable to induce erections without testosterone, as castration eliminates erections even with administration of Oxt and apomorphine; erections can later be re-established with co-administration of testosterone (Melis *et al.*, 1994). Additionally, Oxt interacts with the dopamine and serotonin systems. The dopamine agonist apomorphine injected s.c. induces penile erections in a manner similar to that of Oxt injections into the lateral ventricles (Melis *et al.*, 1989). More recently, Melis and coworkers (Melis *et al.*, 2007) found that: (1) injections of both the Oxt receptor antagonist CPOVT and the dopamine receptor antagonist haloperidol into the shell of the NAcc or the PVN abolishes Oxt-induced penile erections; (2) injections of Oxt into the ventral tegmental area (VTA) increases extracellular dopamine and its metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) in the NAcc, which occurs concomitant with penile erection; and (3) Oxt-containing axons from the PVN to the VTA closely contact dopaminergic neurons in the shell of the NAcc, providing evidence that both dopamine and Oxt influence sexual behavior. Furthermore, i.c.v. injections of CPOVT dose-dependently inhibit the sexual response (erection) normally occurring in response to the dopamine D3 receptor agonist 7-OH-DPAT (Clement *et al.*, 2008).

Serotonin depletion is an underlying factor in premature ejaculation in rats (Olivier *et al.*, 2006) and humans (reviewed in (Giuliano and Clement, 2006). Pharmacological studies indicate that treatment with selective serotonin reuptake inhibitors induce serotonin and Oxt release, which may help to maintain erections and delay ejaculation (reviewed in (de Jong *et al.*, 2007).

Potential interactions between Oxt and nitric oxide (NO) systems in mediating penile erections have been the subject of investigation. Administration of NO synthesis inhibitors (NG-nitro-L-arginine methyl ester and NG-monomethyl-L-arginine), and the oxytocin antagonist CPOVT into the PVN all prevent Oxt-induced erections (Argiolas & Melis, 1995). However, subsequent studies indicate that the same antagonist only prevents erections when injected into the lateral ventricles (Melis *et al.*, 1999). Injections of Oxt into the VTA stimulate dopaminergic neurons that aid in production of NO and ultimately induce penile erection (Succu *et al.*, 2008). However, not all studies agree that the Oxt-NO interaction is necessary for penile erection. Although Oxt i.c.v. increases both the number of erections and the concentration of NO₂- and NO₃- in the PVN (Melis *et al.*, 1997), administration of oxytocin antagonist CPOVT into the lateral ventricles reduces non-contact erections without modifying NO₂- and NO₃- concentrations (Melis *et al.*, 2000).

Finally, Oxt KO males produce normal litters when mated (Nishimori *et al.*, 1996; Young *et al.*, 1996b), indicating apparent normal sexual behavior, and the KOs are still potent sexual triggers to hormone-primed females (Agmo *et al.*, 2008). Therefore, other hormones and mechanisms are more critically involved in sexual behavior in males. For review, see (Argiolas and Melis, 2004, 2005; Carter, 1992).

2.1.3.2 Sex behavior in females: Oxt acts in females to coordinate the onset of sexual maturity through interactions with gonadotropin-releasing hormone (GnRH): treatment with the Oxt antagonist desGly-NH₂-d(CH₂)₂[D-Tyr², Thr⁴]-vasotocin for 6 days significantly decreases GnRH pulse frequency, as well as age of vaginal opening and first estrus (Parent *et al.*, 2008). Upon entering sexual maturity, female sexual behavior is examined in rodents primarily via examining the lordosis response. Lordosis is a reflexive posture displayed by receptive females in response to male mounting, and is primarily under control of E (see (Kow and Pfaff, 1998) for review).

Oxt also induces female sexual behavior, primarily by actions in the mPOA of the hypothalamus and the VMH (both regions underlie lordosis display; see Kow & Pfaff, 1998). Oxt immunoreactivity is enhanced by E (Caldwell *et al.*, 1989a), and E increases affinity for Oxt in the mPOA (Caldwell *et al.*, 1994b). Similarly, Oxt release in the VMH due to mounting by males occurs only in females pretreated with E and P (Caldwell *et al.*, 1989b). In females pretreated with E and P, Oxt injection into the mPOA significantly increases sexual receptivity as measured by the lordosis quotient (LQ: number of lordosis postures/100 mounts), while Oxt injection into the VMH increases lordosis duration only (Schulze and Gorzalka, 1991). Oxt injection into the mesencephalic central gray, or ventral tegmental area (other regions implicated in lordosis behavior) is not shown to alter LQ (Caldwell *et al.*, 1989b).

Oxt facilitates sexual receptivity as measured by an increase in lordosis behavior, but only when the females have been pretreated with either E alone (Caldwell *et al.*, 1986b), P alone (Gorzalka and Lester, 1987), or E and P (Arletti *et al.*, 1985; Caldwell *et al.*, 1989a). In intact, non-ovariectomized females, Oxt significantly increases lordosis quotient (LQ) and duration during estrus, when P levels are highest, while the Oxt antagonist CPOVT decreases LQ and duration (Benelli *et al.*, 1994). Similarly, administration of the Oxt antagonist OVTA prior to treatment with P significantly decreases lordosis posturing, and increases duration of fighting with males (Caldwell *et al.*, 1994a), but only when the Oxt antagonist is injected into the mPOA.

Early work indicates that Oxt may primarily affect facilitation of sexual behavior by P. The selective Oxt antagonist OVTA reduces female sexual behavior in females primed with E and P, but not in females primed with E alone (Witt and Insel, 1991). In contrast, a later study indicates that E (conjugated to bovine serum albumin at position 6) and Oxt infusion to mPOA and medial basal hypothalamus significantly increases sexual receptivity (LQ), whereas E and P with Oxt does not (Caldwell and Moe, 1999). However, the Oxt antagonist used by Witt and Insel is also an Avpr1a receptor antagonist (see (Pedersen and Boccia, 2006) for a recent study investigating Avp and Oxt interactions in controlling female sexual behavior). Treatment with the more selective Oxt antagonist AOVT to ovariectomized (OVX) females primed with E significantly decreases LQ, and increases male-directed antagonistic behavior prior to P injection (Pedersen and Boccia, 2002). This Oxt antagonist does not decrease female sexual behavior at 4 and 6 hours after P injection, but does decrease lordosis 8–12 hours after P (Pedersen and Boccia, 2002). It is likely, therefore, that shortly after P injection, Oxt activation facilitates the onset of female sexual behavior, and contributes to maintaining sexual behavior for up to 8 hours.

Prolactin (see Section 1.5) is released in the presence of Oxt (Egli *et al.*, 2004; Samson *et al.*, 1986) and with vagino-cervical stimulation (Erskine and Kornberg, 1992). Prolactin is released

with mating in a twice-daily surge termed pseudopregnancy; females infused with the Oxt antagonist OVTA into the VMH show only a 22% induction of pseudopregnancy, compared with 100% in females infused with control or an Avpr1a antagonist (Northrop and Erskine, 2008).

Oxt regulates female sexual behavior in other rodent species as well. In a manner similar to rats, Oxt infused into the VMH and mPOA induces sexual receptivity (increased duration of lordosis) in female Syrian hamsters (Whitman and Albers, 1995), while the Oxt antagonist OVTA reduces sexual receptivity. As in rats, female hamsters require pretreatment with some combination of E and P for Oxt to exert an effect (Whitman and Albers, 1995).

Unlike rats, prairie voles do not have a spontaneous estrus cycle. Female voles require social interactions with unfamiliar males for sexual behavior to be displayed (Carter *et al.*, 1987). Accordingly, simple injections of Oxt (i.c.v. or i.p.) do not facilitate sexual receptivity in female prairie voles pretreated with E (Witt *et al.*, 1990), and treatment with an Oxt antagonist does not inhibit sexual behavior (Witt *et al.*, 1991). However, in sexually-naïve females (no exposure to males after weaning), daily Oxt injection (s.c.) for 5 days increases the likelihood of mating (compared to saline treated females), and treatment of Oxt with E increases sexual receptivity greater than E alone (Cushing and Carter, 1999). Therefore, prior exposure to Oxt can mimic the effects of social contact on female sexual behavior. Treatment with the Oxt antagonist CPOVT increases the likelihood of carrying a litter to term when the father is removed (a manipulation that ordinarily leaves a 50:50 chance of producing a litter; (Cushing *et al.*, 2005).

2.1.3.3. Human Studies: In men, Oxt can be found in the corpus cavernosum and epididymis of the penis; binding to the Oxt_r in this region may affect contractility (Vignozzi *et al.*, 2004) and subsequent ejaculation (Filippi *et al.*, 2003). Plasma Oxt levels increase during sexual arousal, and orgasm significantly raises levels in men (Carmichael *et al.*, 1987). In men, intranasal inhalation of Oxt significantly increases plasma Oxt and epinephrine levels for at least one hour, and increases self-perception of arousal during masturbation (Burri *et al.*, 2008). Additionally, a recent case study indicates that intranasal Oxt administered during coitus may treat anorgasmia in men in cases where medical conditions, drug abuse, and psychological issues have been ruled out (Ishak *et al.*, 2008).

In women, the primary medical use of Oxt treatment is to bring about labor, as it quickly advances uterine contractions (Carter, 2003). Oxt has also been used to facilitate breast-feeding, as it aids in milk let-down, but its efficacy is uncertain (Anderson and Valdes, 2007). One case study reports that intranasal inhalation of Oxt to stimulate breast-feeding increases vaginal lubrication and feelings of arousal (Anderson-Hunt and Dennerstein, 1994). Furthermore, plasma Oxt levels significantly correlate with higher levels of arousal and lubrication as measured by the Female Sexual Function Index (Salonia *et al.*, 2005). Plasma Oxt levels increase in women during sexual arousal and are elevated further by orgasm (Blaicher *et al.*, 1999; Carmichael *et al.*, 1987).

2.1.4. Aggression—Aggression is part of the complex repertoire of social behaviors that function to increase the likelihood of survival and reproduction. Aggressive behavior occurs in situations of competition (e.g., for food, mates or space) to establish hierarchy in a social group or in defense of altricial young. The type of situation that will elicit aggressive behavior, as well as the behavior display, depends on the species and sex of the animal studied (Miczek *et al.*, 2007). In laboratory settings, rodents are often used to model aggressive interactions (Blanchard and Blanchard, 2003; Blanchard *et al.*, 1975; Malick, 1975; Miczek *et al.*, 2001). In this section, we will describe the role that Oxt plays in male and female aggressive interactions.

2.1.4.1. Animal Models of Aggression in Males: Generally, aggression in male rodents is believed to be heavily under the control of Avp (see (Caldwell *et al.*, 2008) for review). The role of Oxt in controlling aggressive behavior in males is ambiguous and likely depends upon the species used, the test animals' sexual status and the age at which Oxt levels are manipulated. In prairie voles, ventricular delivery of Oxt reduces sexual behavior but has no effect on aggression (Mahalati *et al.*, 1991). Oxt has been shown to affect aggressive behavior in prairie voles after, but not prior to, mating (Winslow *et al.*, 1993b). This effect is not seen in montane voles, a non-monogamous vole species.

Interestingly, male Wistar rats introduced as an intruder to the cage of a singly housed male rat have between two- and five-fold increases in Oxt levels in the SON and anterior ventrolateral portion of the hypothalamus (Engelmann *et al.*, 1999). This suggests that Oxt's role in aggressive encounters may have more to do with the stress response to this type of social interaction than aggression per se. This mirrors the link between maternal aggression and an anxious phenotype reported in female rats (Bosch *et al.*, 2005). However, inducing subordination in males through use of a chronic subordinate housing condition increases anxiety but does not result in a change in hypothalamic Oxt mRNA levels, and slightly decreases hypothalamic Avp mRNA only at 20 days of chronic subordinate housing (Reber and Neumann, 2008).

In male squirrel monkeys pair-housed for a sufficient length of time in which to form a stable dominant-subordinate relationship, Oxt significantly increases sexual and aggressive behaviors in the dominant, but not subordinate male, during interaction with a female (Winslow and Insel, 1991). Similarly, the increase in aggression was blocked following concomitant administration of Oxt and the Oxt antagonist OVTA (Winslow and Insel, 1991).

A clear picture has yet to emerge from studies using transgenic mice. One line with inactivation of the *Oxt* gene is mildly less aggressive than WT or HET controls, and shows no difference in anxiety behavior in an open field (DeVries *et al.*, 1997). In a different line of Oxt KO mice, other researchers have reported increased aggressive behavior in the resident-intruder paradigm and decreased anxiety in the elevated plus maze (EPM) (Winslow *et al.*, 2000). These effects were noted only in KO mice born to obligate mice (KO-KO matings); KO mice, and their WT controls, were cross-fostered to WT mothers. Non-obligates (KO's produced from HET-HET matings) show no reduction in anxiety and a small increase in aggression only on the third aggressive encounter (Winslow *et al.*, 2000). This suggests that the effects on aggression and anxiety are due to the lack of Oxt in the prenatal environment, or an interaction of genotype and the stress of cross-fostering. Elevated levels of aggression are also reported in Oxt knockouts generated from non-obligates, consistent with the idea that a lack of prenatal activation of the Oxt system results in increased adult aggression (Takayanagi *et al.*, 2005).

2.1.4.2. Animal Models of Aggression in Females: Female mammals are most aggressive during the postpartum period. In rodents, the mother will attack an unfamiliar male introduced to the cage for several days after giving birth. This type of aggression, dubbed maternal aggression, is a complex behavior that is influenced by a variety of factors that have been extensively reviewed elsewhere (Lonstein and Gammie, 2002).

There are several brain areas that appear to be critical to the mediation of maternal aggression, including the PVN. The expression of the immediate early gene *c-Fos* is elevated in aggressive, but not non-aggressive, lactating female rats following exposure to intruders, and the immediate early gene *EGR-1* is elevated by aggressive experience above levels associated with lactation in lactating female rats (Gammie and Nelson, 2001; Hasen and Gammie, 2006).

The results from PVN lesions are less clear since not all findings report effects in the same direction. Most do suggest a role for the PVN in maternal aggression, however. Electrolytic lesions of the PVN have been shown to decrease maternal aggression in rats (Consiglio and Lucion, 1996). Ibotenic acid lesions directed at the parvocellular portion of the PVN increase maternal aggression, an effect also obtained by blockade of Oxt synthesis by injection of Oxt antisense mRNA into the same region (Giovenardi *et al.*, 1998). Fiber sparing kainic acid lesions of the PVN fail to reduce aggressive behavior, however (Olazabal and Ferreira, 1997). Both studies used female Wistar rats, lesioned on the second day postpartum (selectively targeting the parvocellular region of the PVN) and tested for maternal aggression within five days of giving birth. Thus, it is difficult to reconcile these two findings. The preponderance of evidence does point to PVN involvement in maternal aggression.

The amygdala is another region with demonstrable involvement in maternal aggression. Aggressive encounters in female rats have been shown to elevate c-Fos and EGR-1 levels in several amygdalar nuclei (Gammie and Nelson, 2000; Hasen and Gammie, 2006). Administration of bicuculline, a GABA antagonist, into the amygdala decreases aggression in lactating rats (Hansen and Ferreira, 1986). Infusion of the dual Oxtr/Avpr1a antagonist d(CH₂)₅[Try(Me)²-Thr⁴-Tyr-NH₂⁹]-vasotocin in the central nucleus of the amygdala (CeA) increases the number of attacks postpartum female rats made against intruders (Lubin *et al.*, 2003). Oxt infused into the CeA and BNST decreases the frequency of biting and frontal attacks (Consiglio *et al.*, 2005). Oxt has the opposite effect in golden hamsters, however. Administration of Oxt into the CeA increases aggression against a male intruder in postpartum females (Ferris *et al.*, 1992). It is unclear whether this difference is species specific or somehow related to dosage.

Oxt may exert its influence on maternal aggression through its role in modulating anxiety. Oxtr are found in the PVN and CeA, two areas that are part of the circuitry mediating anxiety responses. Administration of Oxt in these areas has been linked to increases in maternal aggression (Ferris *et al.*, 1992; Harmon *et al.*, 2002a; Lubin *et al.*, 2003); but see (Consiglio *et al.*, 2005). Moreover, increased levels of aggression and Oxt release are found in lactating rats bred for high levels of anxiety but not in a less aggressive, low anxiety strain (Bosch *et al.*, 2005). This increase in aggressive behavior is blocked in the high anxiety rats by administration of the Oxtr antagonist AOVT but has no effect on the low anxiety group (Bosch *et al.*, 2005). Aggression levels in the low anxiety group are increased by delivery of Oxt to the PVN, however. Thus Oxt may influence anxiety and aggression together in a manner dependent upon circulating levels of Oxt.

2.1.3.3. Oxt and Aggression in Humans: Little is known about the role of Oxt in human aggression. Higher levels of autoantibodies reactive for Oxt are found in males with conduct disorder than in controls (Fetissov *et al.*, 2006). Oxt administration has been shown to reduce amygdalar activity in response to fear-inducing visual stimuli (Kirsch *et al.*, 2005), and anxiety levels appear to be linked to aggression in several animal models (Bosch *et al.*, 2005; Bosch *et al.*, 2007; Winslow *et al.*, 2000). In humans, Oxt may act to decrease anxiety by increasing recognition (Savaskan *et al.*, 2008) and feelings of affiliation (Kosfeld *et al.*, 2005) (see Sections 2.1.1. and 2.1.2).

2.2. Non-social Behavior

In addition to its effects on social behaviors, oxytocin also impacts non-social behaviors such as non-social memory, anxiety, depression, and stress. The following sections will describe the role that Oxt is believed to play in these behaviors in both non-humans (primarily rodents) and humans via clinical studies. The results are summarized in Table 1.

2.2.1. Learning and Memory

2.2.1.1. Rodent studies: Memory processes are highly influenced by neuropeptides. Generally, Avp seems to enhance both non-spatial and spatial memory, likely through connections between the hippocampus and septum (see (Caldwell *et al.*, 2008) for review). In contrast, Oxt seems to attenuate memory processes. Pioneering work by De Wied and colleagues (Bohus *et al.*, 1978; De Wied, 1971; Kovacs *et al.*, 1978) consistently demonstrated that passive avoidance behavior is either unaffected (Bohus *et al.*, 1978; De Wied, 1971), or impaired by administration of Oxt (Kovacs *et al.*, 1978), even when administered at doses equivalent to effective doses of Avp. Specifically, Oxt decreases “step-down latency” (latency to jump off of a platform onto a floor with which the animals had been trained to associate a shock; (Kovacs *et al.*, 1978) and passive-avoidance behavior (latency to enter a dark chamber in which a shock had previously been given (Kovacs *et al.*, 1979). Region-specific effects of Oxt on passive-avoidance behavior are discussed below. For a complete review of this early work see (Kovacs and Telegdy, 1982). Recently, de Oliveria and colleagues also showed that i.p. Oxt administered prior to testing impairs inhibitory avoidance measuring “step-down latency”, without causing increases in anxiety alone (tested on EPM), and with an accompanying decrease in corticosterone levels (de Oliveira *et al.*, 2007). Stress hormones and effects on the hypothalamic-pituitary-adrenal (HPA) axis may, therefore, mediate the amnesic effects of Oxt.

Later research by De Wied and colleagues indicates that Oxt impairs passive avoidance behavior when administered s.c. both after the conditioning trial (post-learning) and one hour prior to the retention trial (pre-retention; (De Wied *et al.*, 1987). Interestingly, fragments of Oxt containing just the C-terminal [Oxt (4–8), Oxt (4–9), Oxt (5–8), Oxt (5–9)] inhibit passive avoidance behavior as well as or better than the ‘parent’ molecule [Oxt (1–9)] (De Wied *et al.*, 1987). Similarly, Oxt (4–9) significantly decreases conditioned freezing behavior (Stoehr *et al.*, 1992). Oxt effects on passive avoidance memory are bimodal, with low doses of Oxt and its C-terminal peptides facilitating, and higher doses inhibiting, passive avoidance behavior (Gaffori and De Wied, 1988). It is not clear how peripheral administration of these peptides could gain entrance to the brain to influence behavior.

The site of injection can also affect Oxt-induced changes in memory. Passive avoidance behavior is impaired with post-learning injections of Oxt in either the dentate gyrus or dorsal raphe nucleus; however, memory is facilitated with Oxt injection into the dorsal septal nucleus (Kovacs *et al.*, 1979). Furthermore, Oxt antiserum injected into dorsal hippocampus, dorsal raphe nucleus, or lateral habenula does not impair passive avoidance (Greidanus and Baars, 1993), contradicting the idea that Oxt is generally an amnesic peptide (reviewed in (Engelmann *et al.*, 1996).

Whether Oxt influences spatial memory is unclear. Oxt are highly expressed in the hippocampus of mice (Insel *et al.*, 1991). Hippocampal slices treated with Oxt *in vitro* maintain long-term potentiation (LTP) significantly longer than untreated slices, and have higher levels of phosphorylated CREB (Tomizawa *et al.*, 2003). Additionally, i.c.v. Oxt into virgin females significantly improves reference memory on the radial arm maze (i.e., fewer entries into arms that never contained food) on retention testing 3 days after acquisition. As anxiety-like and locomotor behaviors were not altered in the open field, it is believed that Oxt acts directly on the hippocampus to affect memory, and not indirectly through amygdala-based effects on anxiety (Tomizawa *et al.*, 2003). Furthermore, Oxt seems to underlie parity-induced enhancements to spatial memory, as multiparous females treated with the Oxt antagonist CPOVT had significantly lower long-term LTP and phosphorylated CREB, as well as poorer reference memory on the radial arm maze (Monks *et al.*, 2003; Tomizawa *et al.*, 2003).

In other brain regions, Oxt also appears to inhibit spatial memory. Injections of Oxt into the nucleus basalis of Meynert (NBM), a region that provides primary cholinergic pathways to the cortex and is involved attention and memory (Wenk, 1997), significantly increases latency to escape onto the hidden platform in the Morris water maze (MWM) (Wu and Yu, 2004). Furthermore, injection of the Oxt antagonist Atosiban into the NBM blocks the Oxt induced impairment, indicating that action at the Oxt_r in the NBM is responsible for inhibition of spatial memory (Wu and Yu, 2004). Interestingly, mice lacking the Oxt gene throughout the brain and body do not show deficits on the MWM or Y-maze, indicating that Oxt is not necessary for spatial memory (Ferguson *et al.*, 2000). However, Engelmann and colleagues have recently shown that exposure to the MWM for at least 3 days can significantly increase intra-SON Oxt release (Engelmann *et al.*, 2006). The stress of the MWM could underlie the increased Oxt release, indicating that the MWM is not an optimal test of Oxt effects on spatial memory.

2.2.1.2. Human studies: Similar to rodent studies, the available data in humans indicate that Oxt is generally amnesic in both men and women. Infusion of Oxt into women for therapeutic abortions significantly decreases memory, accuracy, and decisiveness when administered for both four and eight hours (Ferrier *et al.*, 1980). Specifically, word recall ability is decreased (increased number of errors) and picture matching is impaired, i.e., increased number of errors and changes in picture selection (Ferrier *et al.*, 1980). A follow-up study indicates that the treatment itself is not amnesic, as six women undergoing therapeutic abortion without Oxt infusion (treatment otherwise identical to (Ferrier *et al.*, 1980) maintain memory abilities on word recall and picture matching (Kennett *et al.*, 1982). Similarly, in men treated with intranasal Oxt, word recall is significantly impaired in comparison to both placebo controls and subjects administered Lys⁸-vasopressin (Fehm-Wolfsdorf *et al.*, 1984). In particular, the ability to recall the most recent words presented on a list (i.e., the ‘recency effect’) is impaired. Recently, Heinrichs *et al.* (Heinrichs *et al.*, 2004) found that Oxt impairs cued recall, as well as generation of words with reproduction-related meaning, but does not impair generation of “neutral” words. The authors conclude that when greater processing is needed, Oxt selectively impairs implicit word memory based upon the meaning of the words (Heinrichs *et al.*, 2004).

Healthy males given Oxt show deficits in learning processes (Bruins *et al.*, 1992). Initial word storage (correctly remembered words after first presentation) and rate of storage (number of trials to recall words at least once) are significantly impaired, with no differences between groups treated with Oxt, Avp, or placebo in measures of attention or arousal (Bruins *et al.*, 1992). Other studies examining Oxt and Avp effects on physiological arousal (heart rate, blood pressure, etc.) also indicate no change in these measures with Oxt administration (reviewed in (Fehm-Wolfsdorf and Born, 1991). These amnesic effects of Oxt are consistent with direct actions of Oxt on memory processes, but access to the brain remains problematical.

2.2.2 Stress, Anxiety and Depression—All creatures engage in allostatic defense in response to stressors, be they physiological or psychogenic. Myriad neural systems are engaged in this complicated process, and a complete description is beyond the scope of this review. Oxt can modulate the physiological and behavioral responses to stress by direct and indirect modulation of the HPA axis at the level of the hypothalamus, amygdala, BNST and septum. As discussed in this section, Oxt appears to have a dampening effect on stress responses. The circuits involved and the mechanisms by which they achieve their coordinated effect still remain to be elucidated.

2.2.2.1. Hypothalamic-pituitary-adrenal Axis and Oxytocin: Oxt plays a role in HPA activity, both in terms of basal function and stress induced activation (Neumann *et al.*, 2000). Two excellent reviews detail Oxt’s effects on HPA functioning (Engelmann *et al.*, 2004; Neumann, 2002), but we will highlight the salient points here. In general, plasma concentrations of Oxt are increased following physiological and psychological stresses,

including forced swim, restraint, cold stress, shaker stress, hyperosmolarity and social stress (Engelmann *et al.*, 1999; Gibbs, 1984; Hashiguchi *et al.*, 1997; Jezova *et al.*, 1995; Lang *et al.*, 1983; Neumann *et al.*, 2000).

Oxt was originally thought to have an agonistic effect on adrenocorticotropin hormone (ACTH) release and a facilitative effect on corticotropin-releasing factor (CRF)-mediated ACTH release at the level of the pituitary: Oxt administered to superfused hemipituitaries or pituitary cells *in vitro* causes the release of ACTH (Link *et al.*, 1992) and potentiates ACTH release in response to CRF (Antoni *et al.*, 1983; Gibbs *et al.*, 1984; Link *et al.*, 1992). This potentiation of ACTH release is due to Oxt's action at the Avpr1b receptor in the pituitary (Schlosser *et al.*, 1994). I.c.v. Oxt administration decreases plasma ACTH levels in anesthetized rats, possibly by affecting catecholamine levels (Gibbs, 1986). Infusion of the Oxt antagonist AOVY into either the lateral ventricles or directly into the PVN increases basal levels of ACTH, as well as stress induced (e.g., after forced swim or EPM) secretion of ACTH and corticosterone (Neumann *et al.*, 2000).

2.2.2.2. Oxytocin and Anxiety: Oxytocin is thought to work as an anxiolytic as it decreases release of stress hormones in both humans (reviewed in Legros, 2001) and rats (Stachowiak *et al.*, 1995). As stated above (section 2.1.3.1), endogenous release of Oxt in males during mating can reduce anxiety-like behaviors (Waldherr and Neumann, 2007). In male rats, Oxt administration reduces anxiety-like behaviors in a number of behavioral tests (e.g., EPM); in mice, this effect is blocked in some tests by the Oxt antagonist WAY-162720 (Ring *et al.*, 2006). Bilateral Oxt infusions to the PVN produce anxiolytic effects in both the EPM and the light-dark box, likely through activation of the extracellular signal-regulated kinase 1/2 cascade (Blume *et al.*, 2008). However, as mentioned above (section 2.1.4.1), inducing subordination in males through use of a chronic subordinate housing condition increases anxiety but does not result in a change in hypothalamic Oxt mRNA levels (Reber and Neumann, 2008).

Oxt has anxiolytic effects in females as well. Ovariectomized female rats show a dose dependent decrease in plasma corticosterone levels following an auditory stressor after chronic i.c.v. injection of Oxt (Windle *et al.*, 1997). An anxiolytic effect of Oxt is also found when female rats are exposed to a novel environment (Windle *et al.*, 1997). Oxt also has an anxiolytic effect on EPM behavior in female ovariectomized mice, but only with combined E + Oxt treatment (McCarthy *et al.*, 1996). Oxt seems to mediate postpartum reductions in anxiety, as delivery of the Oxt antagonist desGly-NH₂,d(CH₂)₅[D-Tyr²,Thr⁴]OVT in the ventrocaudal periaqueductal gray reduces the percentage of time lactating dams spend in open arms of the EPM, but does not affect virgin females' performance (Figueira *et al.*, 2008).

The anxiolytic properties of Oxt may be mediated, at least in part, via action at the OxtR in the amygdala. Oxt infusion into the amygdala, but not the VMH, has an anxiolytic effect on ovariectomized female rats in an open field (Bale *et al.*, 2001). The amygdala is well known for its role in the acquisition, modulation and storage of emotional memory (Davis and Whalen, 2001; LeDoux, 2007; Pare *et al.*, 2004; Schulkin *et al.*, 2003). Projections from the septum and the amygdala may modulate the HPA axis via connections to Oxt neurons in the PVN and SON (Oldfield *et al.*, 1985). Within the extended amygdala there are many regions with binding sites for Oxt (Veinante and Freund-Mercier, 1997). This includes a population of neurons with OxtR in the lateral portion of the CeA that have inhibitory connections to neurons that excite brainstem areas associated with species-specific defensive responses (Huber *et al.*, 2005). Whether this population of neurons plays a functional role in learned fear behavior has yet to be established, but it is clear that Oxt neurons within the CeA modulate some behaviors such as maternal aggression (Bosch *et al.*, 2005; Consiglio *et al.*, 2005; Ferris *et al.*, 1992; Lubin *et al.*, 2003). A recent study (Yoshida, et al., 2009) in mice indicates that many serotonergic raphe neurons express OxtR and that infusion of Oxt into the median raphe results in serotonin

release. Further, i.c.v. Oxt reduces anxiety that is prevented by i.p. administration of a serotonin 5-HT_{2A/2C} receptor antagonist (Yoshida, et al., 2009).

In terms of trait anxiety, results are mixed. Wistar rats bred for high or low levels of anxiety behavior have similar plasma levels of ACTH, corticosterone and Oxt following an EPM stressor (Landgraf *et al.*, 1999). This suggests that Oxt does not play a role in the anxiety displayed by the high anxiety group. However, transgenic female mice lacking endogenous Oxt do show an anxious behavioral. Virgin female Oxt KO mice tested on the EPM make fewer open arm entries than WT, an effect that is reversed by i.c.v. Oxt administration (Mantella *et al.*, 2003). Corticosterone levels are also higher in KO females following acute and chronic shaker stress, though basal levels remain unaffected (Amico *et al.*, 2004a). In a follow-up study, a similar stressor (insertion of rectal probe to record body temperature) also results in higher levels of plasma corticosterone in female Oxt KO mice compared with WT mice (Amico *et al.*, 2008). Interestingly, a physical stressor (insulin-induced hypoglycemia) does not cause female Oxt KO mice to release greater amounts of corticosterone (Amico *et al.*, 2008), implicating the central Oxt pathways in modulating different types of stressors.

In one line of Oxt KO mice, male offspring of KO-KO parents show reduced anxiety on the EPM, though this effect may be due to lack of exposure to Oxt in utero (Winslow *et al.*, 2000); see Section 2.1.4. for more discussion). Others have reported no effect on anxiety-like behavior in Oxt KO mice or in a partial forebrain-specific Oxt knockout line (Lee *et al.*, 2008). Future work using temporal and spatial KO of Oxt populations in the amygdala, septum and striatum through the use of lentiviral gene delivery, for example, will be useful in clarifying the role of Oxt in anxiety.

2.2.2.3. Human Studies: In humans, intranasal Oxt generally facilitates correct classification of emotional faces into either positive or negative categories (Di Simplicio *et al.*, 2008). Oxt may exert effects on emotionality by acting within the amygdala. Oxt appears to reduce amygdalar activation in response to vague or threatening stimuli and may increase feelings of trust and affiliation by reducing social- or novelty-induced amygdalar activation (Baumgartner *et al.*, 2008; Meyer-Lindenberg, 2008). Intranasal Oxt administration reduces amygdalar activation in response to fearful or threatening scenes (Kirsch *et al.*, 2005). Oxt also modulates amygdalar responses to socially relevant stimuli such as faces (Domes *et al.*, 2007b; Kirsch *et al.*, 2005). Pre-stress intranasal administration of Oxt blunts the social stress of speaking in front of an audience, a situation that increases reported feelings of stress as well as cortisol levels (Heinrichs *et al.*, 2003). The anxiolytic effect of Oxt is enhanced by concomitant social support from a friend prior to the stressor (Heinrichs *et al.*, 2003). Lower plasma Oxt levels have been linked to higher levels of psychological distress and less parental attachment (Gordon *et al.*, 2008). Oxt has also been shown to modulate learning about socially relevant stimuli. Subjects trained using the pairing of a mild shock with images of people directing their gaze towards or away from the observer do not show an increase in reaction time or amygdalar responding above control levels to those images paired with shock (Petrovic *et al.*, 2008). The suppression of amygdalar activity by Oxt is even greater for images with direct gaze than indirect gaze (Petrovic *et al.*, 2008). This suggests that Oxt within the amygdala plays a role in processing negative information about negative stimuli, but Oxt is particularly important for more socially relevant (gaze directed) stimuli.

There is also strong evidence that oxytocin is involved in the regulation of affect in humans. Lower levels of plasma Oxt have been reported in humans with major depression (Scantamburlo *et al.*, 2007) while increased post-mortem levels of Oxt mRNA in the PVN are found in patients with melancholic depression (Meynen *et al.*, 2007). Oxt levels are also negatively correlated with self-reported psychological distress, including depressive symptoms (Gordon *et al.*, 2008). In one study of depressed patients, those with the lowest Oxt plasma

levels also were those least likely to find social interactions rewarding (Bell *et al.*, 2006). Increases in the number of Oxt-ir neurons in the PVN of people with major depression or bipolar disorder have also been reported (Purba *et al.*, 1996).

Increased Oxt levels postpartum have been associated with elevated mood and decreased anxiety. Administration of the Oxt antagonist AOVN increases ACTH levels in lactating rats (Neumann *et al.*, 2001). In humans, breast-feeding similarly decreases cortisol levels while increasing Oxt levels and is associated with a decrease in negative feelings (Mezzacappa and Katlin, 2002). Compared with non-lactating women, postpartum mothers (2 days after birth) who have received Oxt during labor, just after birth, or were not medicated, have significantly lower scores on the anxiety and aggression scales, and higher on the socialization scale, of the Karolinska Scales of Personality (Jonas *et al.*, 2008). Scores remained similar at 2 and 6 months. Women who received epidural analgesia without Oxt did not differ from the non-lactating women at 2 days postpartum but did at 2 and 6 months, suggesting that both exogenous and endogenous Oxt maintain lower anxiety levels and promote sociability in women through the early postpartum period. A recent study of depressed women reveals increased pulsatile variability and total Oxt release during an affiliation-focused image task (Cyranski *et al.*, 2008).

2.2.2.5. Conclusion: Both physiological and psychological stressors increase Oxt plasma concentrations and central release in a few key brain regions. This increase dampens the release of HPA axis-mediated stress hormones and creates an anxiolytic behavioral profile. Oxt imbalances have been associated with both anxiety and depression, though direct evidence for Oxt's role as a therapeutic agent is still awaited. Given the presence of Oxt receptors in the hypothalamus and extended amygdala and its link to HPA function and mood, there is potential for therapeutic use of Oxt in mood disorders.

2.3. Other Behavioral Effects

2.3.1. Oxytocin and feeding behavior—Oxt regulates intake of food and various other solutions, such as NaCl and sucrose. Generally, Oxt suppresses food intake, while at the same time facilitating the onset of sexual behavior. Appetitive control may occur, in part, in the VMH through hormonal like actions after Oxt release from PVN and SON magnocellular dendrites and possibly by yet-to-be-discovered synaptic contact from PVN parvocellular fibers (reviewed in (Leng *et al.*, 2008b; Sabatier *et al.*, 2007). Oxt parvocellular fibers project to the nucleus of the solitary tract as well where regulation of feeding may occur (Blevins, *et al.*, 2003). Oxytocin is also co-expressed with the satiety factor nesfatin-1 in about a quarter of PVN Oxt neurons and 35% of SON Oxt neurons (Kohno *et al.*, 2008). Centrally-administered Oxt and Oxt agonists i.c.v. strongly inhibit feeding (Olson *et al.*, 1991), as does i.p. Oxt, albeit in a dose-dependent manner, with the highest doses most strongly inhibiting food intake (Arletti *et al.*, 1989, 1990). Oxt antagonists prevent this inhibition (Arletti *et al.*, 1989, 1990; Olson *et al.*, 1991). Furthermore, Oxt dose-dependently inhibits water intake in freely-drinking animals, as well as induces thirst (Arletti *et al.*, 1990). During pregnancy, activity of magnocellular Oxt neurons is reduced and Oxt release is inhibited, which may contribute to hyperphagia during pregnancy (Douglas *et al.*, 2007).

Oxt is implicated (along with neuropeptide Y and orexin) in ingestion of sugar, as during a one hour scheduled intake of palatable sucrose pellets, Oxt gene expression is significantly up-regulated in the hypothalamus (Olszewski *et al.*, 2009). However, Oxt KO mice maintain appetite after dehydration, whereas WT littermates do not (Rinaman *et al.*, 2005). Furthermore, compared to WT mice, Oxt KO mice increase ingestion of a sodium (NaCl) solution (Amico *et al.*, 2003), sucrose and saccharine solutions (Amico *et al.*, 2005; Billings *et al.*, 2006), and both sweet and non-sweet carbohydrate solutions (Sclafani *et al.*, 2007), with only an initial

(but not sustained) preference for a palatable fat-containing solution (Miedlar *et al.*, 2007). Oxt KO mice show slightly increased weight gain over WT, as well as impaired thermoregulation when exposed to cold (Kasahara *et al.*, 2007). Oxt mRNA and peptide are depleted by approximately 80% in Sim-1 haploinsufficient mice, which have abnormal makeup of the PVN (including PVN neuropeptides) and are severely obese (Kublaoui *et al.*, 2008; Michaud *et al.*, 2001). Treatment with Oxt inhibits food intake in Sim-1 haploinsufficient mice (Kublaoui *et al.*, 2008).

Some evidence indicates that the Oxt_r is also involved in feeding behavior. Oxt_r WT and KO mice do not differ in overall daily food intake (Leng *et al.*, 2008b; Takayanagi *et al.*, 2008), but late-onset obesity (beginning after 12 weeks old) is observed in Oxt_r KO males, and is likely due to heavier fat tissue (Takayanagi *et al.*, 2008). In contrast, no weight differences are found between KO and WT in a different line of Oxt_r mice, and partial forebrain-specific Oxt_r KO male and female mice (Oxt_r^{FB/FB}) weigh significantly less than WT littermates (Lee *et al.*, 2008).

2.3.2. Oxytocin and pain perception—Pain perception is generally measured in rodents through the tail flick test, in which heat is applied to the tail and latency to remove the tail from the heat source is measured. The hot plate test is also used and the latency for the animal to lick his paw, vocalize or jump is measured. Oxt lowers the pain threshold in rats, after either i.c.v. or intra-spinal administration (Yang *et al.*, 2007a, b). Specifically, Oxt increases latency to remove the tail from heat, while the Oxt antagonist CPOVT prevents the antinociceptive properties of Oxt (Arletti *et al.*, 1993; Lundeberg *et al.*, 1994; Uvnas-Moberg *et al.*, 1992). Oxt KO mice have significantly reduced antinociception following stress compared to WT mice, and the Oxt antagonist CPOVT given to WT mice attenuates antinociception (Robinson *et al.*, 2002). Recent research indicates that central Oxt (i.c.v. or intra-spinal) combined with acupuncture treatment significantly increases the pain threshold in compared to non-treated controls (Yang *et al.*, 2007b). Oxt seems to mediate antinociception by connections from Oxt neurons in the PVN to the dorsal horn of the spinal cord (Robinson *et al.*, 2002), specifically by acting upon a subpopulation of lamina II glutamatergic interneurons in the dorsal horn. This generally elevates inhibition at the level of the spinal cord (Breton *et al.*, 2008). Furthermore, pain stimulation decreases Oxt concentration throughout the brain, particularly in hypothalamic regions, although notably not in the PVN (Yang *et al.*, 2007a, b).

Interestingly, a recent study reports that Oxt may underlie ethnic differences in pain perception. African American and non-Hispanic white women given three types of pain-testing procedures display differences in overall tolerance to pain that are correlated with the amount of basal Oxt (Grewen *et al.*, 2008). Oxt levels are also correlated with other measures of pain perception and tolerance, such as norepinephrine and beta-endorphin levels (Grewen *et al.*, 2008).

2.3.3. Oxytocin and grooming—Oxt administered i.c.v. dose-dependently enhances grooming activity in both male and female rats, as does s.c. Oxt, albeit not as strongly (Drago *et al.*, 1986b). Other studies confirm the relationship between Oxt and increased grooming (Caldwell *et al.*, 1986a; Drago *et al.*, 1986a), and find that select brain regions seem to control Oxt-mediated grooming behavior, including the NAcc (Drago *et al.*, 1986a), various hypothalamic nuclei (the so-called “hypothalamic grooming area”, which includes the VMN and dorsal hypothalamic area; Kaltwasser and Andres, 1989; Roeling *et al.*, 1993), and most notably the ventral tegmentum (Kaltwasser and Andres, 1989; Kaltwasser and Crawley, 1987; Stivers *et al.*, 1988). Furthermore, i.c.v. Oxt significantly increases grooming in Oxt KO mice to greater levels than in WT mice (Amico *et al.*, 2004b). Oxt elicits its effects on grooming by action at the Oxt_r, as the Oxt antagonist Atosiban abolishes Oxt, but not Avp, effects on grooming (Amico *et al.*, 2004b). Oxt also seems to underlie grooming of offspring, as

administration of an Oxt antagonist increases self-grooming in lactating dams, redirecting grooming behavior from pup-focused to self-focused (Pedersen and Boccia, 2003).

Hypergrooming is one component of animal models of obsessive-compulsive disorder (OCD) (Berridge *et al.*, 2005). As Oxt elevates grooming, and has been shown to be elevated in CSF levels of patients with OCD (Leckman *et al.*, 1994b), some have proposed that Oxt may mediate some forms of OCD (Leckman *et al.*, 1994a). However, not all studies have found elevated Oxt in OCD patients (Altemus *et al.*, 1999), and whether intranasal Oxt can improve OCD symptoms remains unclear (Anseau *et al.*, 1987; den Boer and Westenberg, 1992). Recently, an Oxt-induced hypergrooming model of OCD was developed by Oxt administration to the CeA (Marroni *et al.*, 2007). Oxt in the CeA significantly increases all components of grooming, likely through connections from the CeA to the hypothalamic grooming area (Marroni *et al.*, 2007).

3. Implications for human behavior

3.1. Love, bonding, and Trust

While many studies indicate Oxt as a facilitator to pair bonding and parental care in animal studies (see Sections 2.1.2.), data from human studies is inconclusive. Generally, it is believed that Oxt facilitates social interactions and feelings of attachment in humans. Heterosexual couples receiving intranasal Oxt prior to a videotaped “conflict discussion” display significantly increased positive communication behaviors (such as eye contact, self-disclosure, and positive body language) than couples treated with placebo (Ditzen *et al.*, 2008). Oxt further strengthens the anxiolytic effect of social support (presence of a friend) during the Trier Social Stress Test (public speaking and arithmetic in front of an audience), as measured by decreased corticosterone in men (Heinrichs *et al.*, 2003). In women, Oxt is positively correlated with higher self-reported feelings of attachment (tendency to express and share emotions) on the Temperament and Character Inventory (Tops *et al.*, 2007). Women viewing pictures of loved ones have high brain activity in dopaminergic pathways associated with reward, which also contain high levels of Oxt and Avp receptors (Bartels and Zeki, 2004), as do people self-describing as being “intensely in love” (Fisher *et al.*, 2005; Fisher *et al.*, 2006). However, no study has conclusively shown that being in a relationship, or “in love,” is associated with high levels of Oxt (reviewed in (Campbell, 2008). Interestingly, dog owners who receive a “long” duration of gaze from their dogs, and report a high degree of attachment to their dogs, have higher urinary Oxt (but not Avp) levels after interacting with the dogs than owners receiving “short” duration of gaze and who report a lower degree of attachment (Nagasawa *et al.*, 2008). This study indicates that Oxt may be involved in other forms of bonding, such as owner-pet, although little other evidence exists to support this idea.

Greater evidence implicates Oxt in human maternal care. Oxt levels are very stable throughout all trimesters of pregnancy, and are positively associated with maternal-fetal attachment as measured by the maternal-fetal attachment scale (self-reported feelings regarding the mothers’ views of their fetus; (Levine *et al.*, 2007). Oxt levels in the first trimester and early postpartum period have been positively correlated with certain maternal bonding behaviors, such as gaze with infant, vocalizations to infant, and affectionate touch (Feldman *et al.*, 2007). Viewing images of their children activates dopaminergic pathways in the mothers’ brains associated with reward that also contain high levels of Oxt and Avp receptors (Bartels and Zeki, 2004). Mothers with variants of the serotonin transporter and the Oxt genes (the *5-HTT SLC6A4* and *OXT* *rs53576* polymorphisms, respectively) show lower levels of sensitive responsiveness to their toddlers (rated by observers on the aid given by the mothers to their children on cognitively difficult tasks (Bakermans-Kranenburg and van Ijzendoorn, 2008), implicating systems involved in production and bonding of Oxt in maternal responsiveness. The effect of the *rs53576* polymorphism on Oxt pharmacology is not known.

As adults, plasma Oxt levels are positively correlated with self-report of the affiliative bond to the subjects' parents, and negatively correlated to reports of depression and anxiety (Gordon *et al.*, 2008). In men with early parental separation (long-term separation from at least one parent due to divorce or death prior to age 13), Oxt does not decrease salivary cortisol levels as in control males, indicating a possible abnormal HPA response to Oxt in these subjects (Meinlschmidt and Heim, 2007). Additionally, it is unclear what effects, if any, exposure to Oxt during breast-feeding could possibly have on development of the offspring (reviewed in Carter, 2003). It is possible that Oxt may promote parental care and subsequent feelings of attachment in both the parent and the offspring; however, more study is needed.

Recent work has focused on one route in which Oxt promotes sociability: by increasing feelings of trust. Zak and colleagues have implemented a money transfer game, in which Subject 1 (investor) sends some quantity of money (through a computer) to Subject 2 (trustee), who is told that Subject 1 sent the trustee money. Both subjects are aware that the amount sent will be tripled, and that Subject 2 will be prompted to send an amount back to Subject 1. Trustworthiness is measured by the amounts sent from investor to trustee, and back to investor (Zak, 2008). Plasma Oxt levels are higher in Subject 2 when Subject 1 chooses how much to give (an intentional signal of trust) than when the amount Subject 1 sends is randomly assigned (Zak *et al.*, 2004, 2005), although it should be remembered that peripheral peptide levels do not necessarily reflect central levels (Bartz and Hollander, 2006).

When given intranasal Oxt 50 minutes prior to testing, the average amount of money given by Subject 1 is substantially higher than with placebo treatment (Kosfeld *et al.*, 2005). Interestingly, when subjects play the same game but send money to a "project", not a "trustee", Oxt does not increase the amount of money sent, so overall risk-taking behavior is not increased by intranasal Oxt (Kosfeld *et al.*, 2005). Intranasal Oxt maintains trusting behavior, even when subjects learn that their trust has been breached (i.e., "trustee" fails to return money 50% of the time; Baumgartner *et al.*, 2008). Furthermore, Oxt decreases activity in the amygdala, caudate nucleus, and midbrain regions compared to placebo, indicating that these regions modulate Oxt effects on trust (Baumgartner *et al.*, 2008). Similar to the trust game, intranasal Oxt increases generosity (Subject 1 gives money to Subject 2 while taking into consideration the amount Subject 2 finds acceptable), but not overall altruism (Subject 1 gives to Subject 2 with no feedback from Subject 2; Zak *et al.*, 2007). Therefore, Oxt seems to particularly affect the ability to understand others' emotions, i.e., affects empathy.

Intranasal Oxt increases the amount of time spent gazing at the eye region of human faces (Guastella *et al.*, 2008a) as well as the likelihood of recalling a happy face (Guastella *et al.*, 2008b). Intranasal Oxt also improves the ability to infer the mental state of others from social cues in the eye region (Domes *et al.*, 2007b). Similarly, intranasal Oxt attenuates feelings of negativity towards faces conditioned with negative affective ratings, particularly in faces with direct gaze (Petrovic *et al.*, 2008). Oxt may thus increase feelings of trust and empathy by increasing eye gaze and subsequent understanding of social cues. Overall, this line of research indicates that Oxt enhances feelings of generosity, trust, and may aid in detection and understanding of others' feelings (empathy).

3.2. Autism

Autism is a neuropsychological disorder characterized by abnormal social relationships, including impaired interaction and communication, as well as repetitive and stereotyped behaviors. Autism spectrum disorders (ASD; includes autism) are labeled as pervasive developmental disorders, and can include other medical disorders, such as retardation and seizures, and psychological problems, such as heightened anxiety (Fombonne, 2005). Recently, much effort has gone into determining the underlying causes of autism and related disorders. The positive relationship between Oxt and formation of social bonds in animal studies

(reviewed in (Hammock and Young, 2006) has led many to believe that Oxt abnormalities may play a part in autism. Indeed, several studies indicate that single nucleotide polymorphisms (SNPs) in the *Oxt* (Yrigollen *et al.*, 2008) and *Oxtr* genes (Jacob *et al.*, 2007; Lerer *et al.*, 2008; Wu *et al.*, 2005) are linked with ASD. Intravenous infusion of Oxt into adults with autism and Asperger's disorder significantly reduces both number and severity of repetitive behaviors (such as repeating, self-injury, touching; (Hollander *et al.*, 2003), and increases ability to comprehend and remember the affective component of spoken words (happy, indifferent, angry, or sad; (Hollander *et al.*, 2007).

However promising the link between Oxt and autism may be, it is important to remember that many gene systems, in many combinations, contribute to any observable phenotype, and that many systems are currently being explored in relation to autism (Abu-Elneel *et al.*, 2008; McCauley *et al.*, 2005; Morrow *et al.*, 2008; Yan *et al.*, 2008). For a recent review of the possible link between Oxt and autism, as well as other neuropsychiatric disorders, see (Marazziti and Dell'osso, 2008).

3.3. Oxytocin and schizophrenia

Prepulse inhibition (PPI) of the startle reflex is a form of sensorimotor gating displayed across a variety of species in which the reflexive reaction to a sudden, intense sensory stimulus is reduced by a preceding, weaker sensory stimulus. This gating process is an attentional mechanism that filters potentially distracting stimuli so that attention can be focused on relevant information. Deficits in sensorimotor gating are a feature of many psychiatric and neurological disorders including schizophrenia (Braff *et al.*, 2001; Braff *et al.*, 1992; Grillon *et al.*, 1992; Light and Braff, 1999). Using animal models, PPI has been disrupted in a manner similar to that seen in schizophrenics by the administration of psychotomimetic drugs (Davis *et al.*, 1990; Mansbach *et al.*, 1989; Mansbach and Geyer, 1989; Mansbach *et al.*, 1988), particularly those that affect the dopamine and glutamate/NMDA receptors (Martinez *et al.*, 2000).

Oxt levels may be elevated in patients with psychiatric disorders such as schizophrenia (Beckmann *et al.*, 1985) and OCD (Leckman *et al.*, 1994b), although not all studies find such a difference (Glovinsky *et al.*, 1994). Also, a recent study reports lower levels of Oxt in hyponatremic schizophrenics who display altered HPA activity (Goldman *et al.*, 2008). However, use of antipsychotics such as amperozide (serotonin antagonist) and clozapine (dopamine and partial serotonin agonist) significantly increases plasma Oxt levels (Uvnas-Moberg *et al.*, 1992), indicating that Oxt may act as a natural antipsychotic. Indeed, Oxt restores PPI that is disrupted by dizocilpine (non-competitive NMDA antagonist) and amphetamine (indirect dopamine agonist) (Feifel and Reza, 1999). Furthermore, Oxt KO mice exhibit greater PPI deficits with treatment of phencyclidine (PCP, an NMDA antagonist) than do WT mice (Caldwell *et al.*, 2009), indicating that Oxt in particular affects the glutamatergic component of PPI, and likely underlies disruptions in sensory gating observed in schizophrenic patients (Swerdlow *et al.*, 2006).

In addition to disrupting PPI, chronic PCP (14 days) causes social deficits and decreased Oxt binding in the hypothalamus, but increases Oxt binding in the CeA; bilateral Oxt administered to the CeA reverses the social deficits from PCP (Lee *et al.*, 2005). Interestingly, levels of plasma Oxt in schizophrenics positively predicts their ability to identify facial emotions (Goldman *et al.*, 2008), further implicating Oxt in the social aspects of schizophrenia.

4. Concluding Remarks

In the current review, we have detailed the role of Oxt in a variety of behaviors, including recognition of previously met conspecifics, affiliation, sexual behavior, and reduction of anxiety. In light of the prominent role in parturition and essential role in lactation, we are drawn

to the view that Oxt serves the continued propagation of a species. As indicated in Figure 5, the cycle of life has numerous points at which Oxt intercedes. In ancient species such as earthworms, leeches, and gastropods, progenitors of Oxt were likely involved in reproduction (Fujino *et al.*, 1999; Oumi *et al.*, 1996; Satake *et al.*, 1999; Van Kesteren *et al.*, 1995). Amazingly, through eons of evolution, Oxt's repertoire has expanded to maintain a central role in more complicated aspects of reproductive behavior. For these reasons, we call Oxt the great facilitator of life.

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Abbreviations

ACTH	adrenocorticotropin hormone
AOVT	desGly-NH ₂ ,d(CH ₂) ₅ [Try(Me) ² ,Thr ⁴ ,Orn ⁸]vasotocin
Avp	vasopressin
Avpr	vasopressin receptor
BNST	bed nucleus of the stria terminalis
CeA	central nucleus of the amygdala
CPOVT	d(CH ₂) ₅ [Tyr(Me) ² -Orn ⁸]vasotocin
CRF	corticotropin-releasing factor
CSF	cerebrospinal fluid
E	estrogen
EB	estradiol benzoate
EPM	elevated plus maze
ERE	estrogen-response element
FB	forebrain
GnRH	gonadatropin-releasing hormone

HET	heterozygous
HPA	hypothalamic-pituitary-adrenal
i.c.v	intracerebroventricular
IGR	intergenic region
i.p	intrperitoneal
ir	immunoreactive
KO	knockout
LQ	lordosis quotient
mPOA	medial preoptic area of the hypothalamus
MWM	Morris water maze
NAcc	nucleus accumbens
NBM	nucleus basalis of Meynert
NE	norepinephrine
OB	olfactory bulb
OCD	obsessive compulsive disorder
OVTA	d(CH ₂) ₅ [Try(Me) ² ,Thr ⁴ ,Orn ⁸ ,Tyr ⁹ -NH ₂]-vasotocin
OVX	ovariectomized
Oxt	oxytocin
Oxtr	oxytocin receptor
P	progesterone

PCP	phencyclidine
PPI	prepulse inhibition
PVN	paraventricular nucleus of the hypothalamus
s.c	subcutaneous
SON	supraoptic nucleus
VMH	ventromedial hypothalamus
VTA	ventral tegmental area
WT	wildtype

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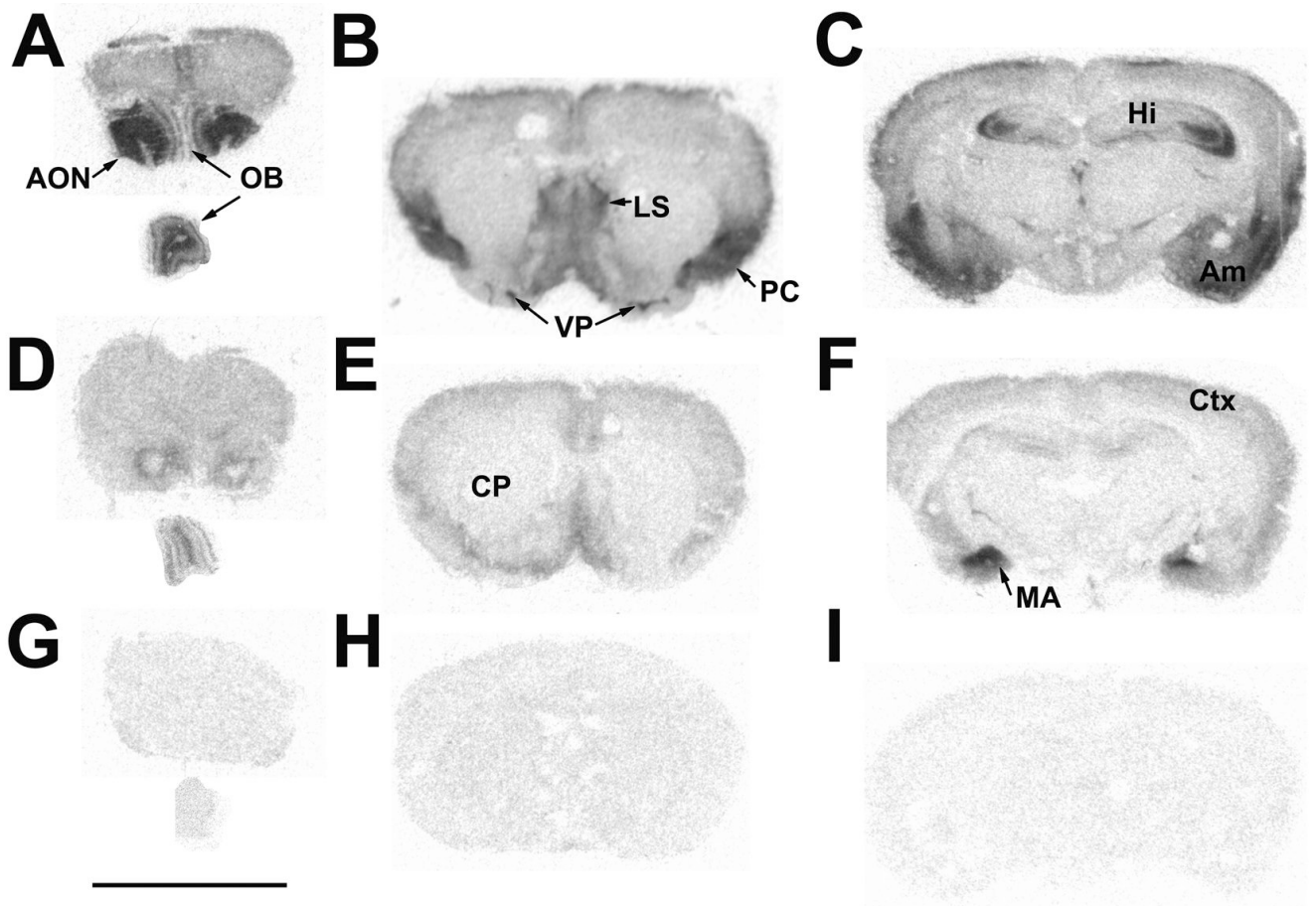


Fig. 2. Disruption of the *Oxtr* in mouse forebrain by *Camk2a*-driven Cre recombinase expression. *Oxtr* levels were examined by receptor binding in coronal sections from adult WT (A, B, C), *Oxtr*^{FB/FB} (D, E, F), and *Oxtr*^{-/-} (G, H, I) mice. Most areas in the forebrain of *Oxtr*^{FB/FB} mice show decreased levels of binding, with the notable exception of the medial amygdala (MA). *Oxtr*^{-/-} mice show only background levels. Exposure was for 3 weeks to X-ray film (C). Abbreviations: Am, amygdala; AON, anterior olfactory nucleus; CP, caudate-putamen; Ctx, cerebral cortex; Hi, hippocampal formation; LS, lateral septum; MA, medial amygdala; OB, olfactory bulb; PC, piriform cortex; VP, ventral pallidum. Scale bar equals 0.5 cm. From (Lee *et al.*, 2008).

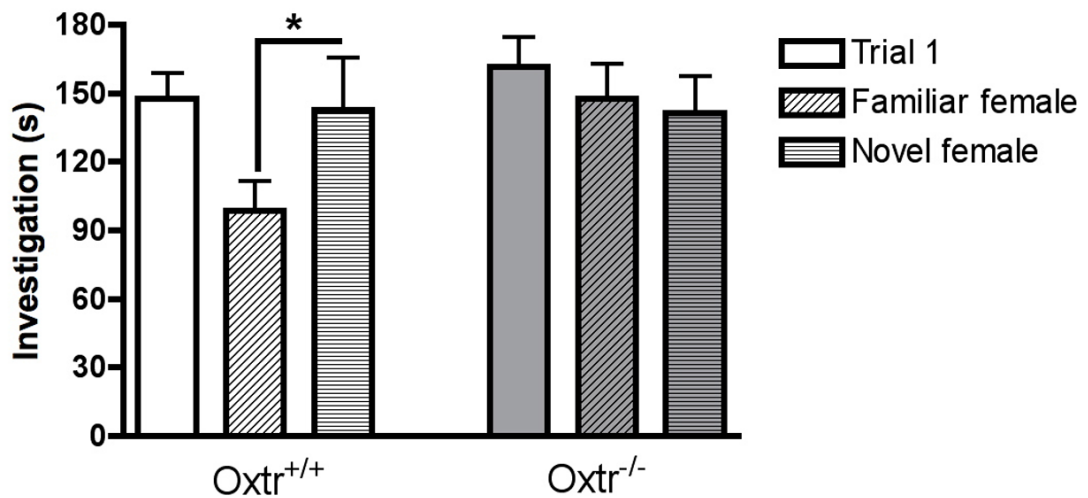


Fig. 3.

Social recognition by *Oxtr* WT and KO males, as examined with the two-trial social recognition task. Investigation times of stimulus females during Trial 1 were equal across genotypes, indicating no motivational or olfactory differences. During Trial 2, *Oxtr* WT males display remember the previous stimulus females, represented by significantly less time investigating those female from Trial 1 (“familiar”) as compared to new females (“novel”); * $p < 0.05$ by t -test between familiar and novel. In contrast, *Oxtr* KO males spend equal times investigating the “familiar” and “novel” females, indicating a reduced ability to remember the familiar female and impaired social recognition. Adapted from (Lee *et al.*, 2008).

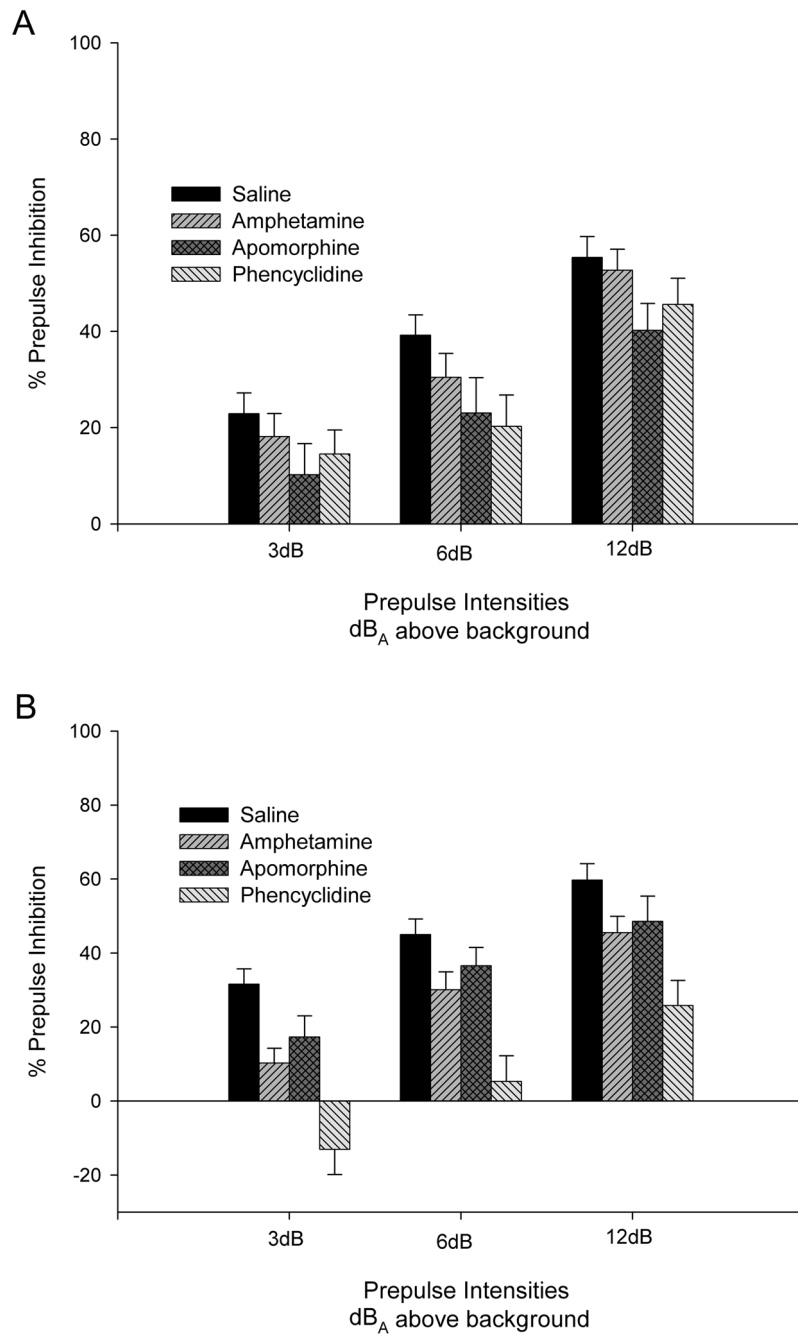


Fig. 4. The effects of treatment with saline, 10 mg/kg of amphetamine, 10 mg/kg of apomorphine, or 6 mg/kg of phencyclidine on the prepulse inhibition of the startle reflex (PPI) percentage in Oxt WT (A) and KO (B) mice. Data were analyzed using a repeated measures analysis of variance. There were main effects of drug treatment, but not genotype. Compared to saline, treatment with amphetamine, apomorphine, and phencyclidine all had an effect on PPI percentage and there was a prepulse intensity-dependent increase in PPI percentage across all groups. There was an interaction between drug and genotype. Specifically, in Oxt KO mice, treatment with phencyclidine resulted in impaired PPI compared to saline treatment in Oxt WT mice. From (Caldwell *et al.*, 2009).

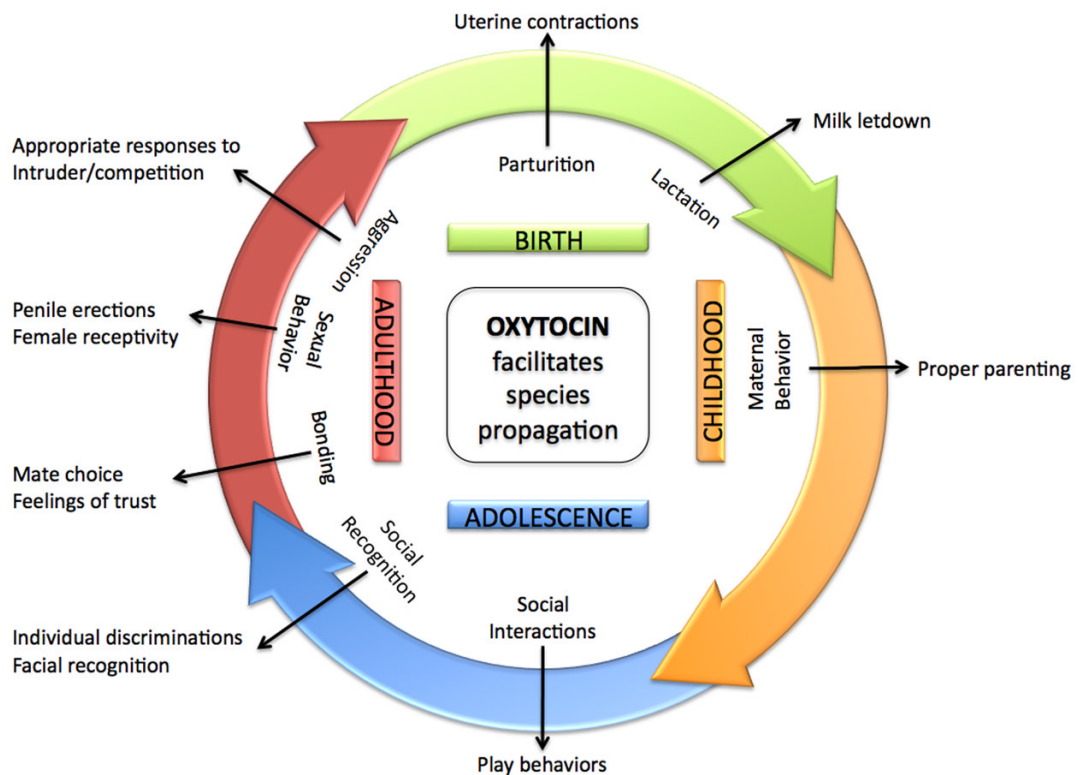


Fig. 5. A simple cycle of life illustrates numerous points at which Oxt may affect behaviors and physiology to facilitate the propagation of the species.

Table

Summary of the behavioral effects of Oxt and the Oxtr

Behavioral Classes	Behaviors	Effects of Oxt in rodents	Effects of Oxt in humans
<i>Social Behaviors</i>			
Social memory	Social recognition	--↑ odor processing in olfactory bulb --↑ social memory --↓ social recognition in Oxtr KO mice -- abnormal Bruce effect in female Oxt KO mice	--↓ amygdalar activation to social stimuli --↑ memory for faces
Affiliation	Sexual behavior	--↑ erections (with T) and ejaculation frequency in males --↑ receptivity (with E) in females	--↑ arousal in men and women --↑ uterine contractions at parturition
	Paternal behavior	--↓ parental behavior with concomitant Avp/Oxt antagonism	no known effect
		--↓ adult paternal behavior with Oxt antagonist on PND1	
	Maternal behavior	--↑ Oxtr throughout the brain with onset of maternal behavior -- necessary for lactation -- induces full repertoire of maternal behaviors (in presence of E) --↓ pup retrieval and pup survival in Oxtr KO	no known effect
Aggression	Female aggression	--↑ Oxt levels in CeA correlated with aggression	no known effect
	Male aggression	-- may have organizational effect during prenatal period	--↑ plasma Oxt levels in males with conduct disorder
<i>Non-Social Behavior</i>			
Learning and Memory	Non-spatial memory	--↓ memory in passive avoidance tasks	--↓ episodic memory in men and women --↓ verbal recall of certain categories of words
	Spatial memory	--↑ memory when injected into hippocampus --↓ memory when injected into NBM	no known effect
Anxiety & Depression	Anxiety	--↓ anxiety following Oxt administration --↑ anxiety in some Oxtr KO mice; sexually dimorphic	--↓ amygdalar response to threatening stimuli --↓ anxiety to social stressors
	Depression	--↑ active/coping behaviors with i.p. Oxt administration	--↓ plasma Oxt associated with major depression