

OXYTOCIN PATHWAYS AND THE EVOLUTION OF HUMAN BEHAVIOR

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■ **Abstract** This review examines the hypothesis that oxytocin pathways---which include the neuropeptide oxytocin, the related peptide vasopressin, and their receptors---are at the center of physiological and genetic systems that permitted the evolution of the human nervous system and allowed the expression of contemporary human sociality. Unique actions of oxytocin, including the facilitation of birth, lactation, maternal behavior, genetic regulation of the growth of the neocortex, and the maintenance of the blood supply to the cortex, may have been necessary for encephalization. Peptide-facilitated attachment also allows the extended periods of nurture necessary for the emergence of human intellectual development. In general, oxytocin acts to allow the high levels of social sensitivity and attunement necessary for human sociality and for rearing a human child. Under optimal conditions oxytocin may create an emotional sense of safety. Oxytocin dynamically moderates the autonomic nervous system, and effects of oxytocin on vagal pathways, as well as the antioxidant and anti-inflammatory effects of this peptide, help to explain the pervasive adaptive consequences of social behavior for emotional and physical health.

Keywords vasopressin, social behavior, neocortex, autonomic nervous system

OVERVIEW

Humans have a history of within-species aggression, abuse, and warfare, which continues to this day. However, we also are the primate species that relies most strongly for its survival on social intelligence and social communication (Hrdy 2009).

In the absence of social interactions, humans typically cannot reproduce, thrive, or even survive. Without formal training, most humans nurture their children, care for the infirm, and share joy in the accomplishments of others. How does this happen and why?

The purpose of this review is to examine the hypothesis that the mammalian neuropeptide, oxytocin, had a permissive role in the evolution of the human nervous system and continues to play a central role in the expression of the high levels of sociality that are essential to contemporary human behavior. Specifically, I propose that in humans our large cortex, high levels of social cognition, and complex social interactions and social bonds could not have evolved without the physiological and behavioral functions of oxytocin.

Of particular relevance to the evolution and expression of primate sociality are selective social interactions, which in turn rely on social sensitivity, cognition, and communication (Seyfarth & Cheney 2012). Oxytocin is at the core of the anatomical and physiological substrates for mammalian reproduction. The mammalian brain and pelvis can be physically remodeled by the actions of oxytocin. Oxytocin is permissive for birth and is probably of special importance to species, including primates, in which infants have large heads. Oxytocin helps to protect the brain from hypoxia, especially during birth (Khazipov et al. 2008). Through lactation and prolonged periods of postnatal nurture and later social interactions, oxytocin shapes the physical development of the human neocortex as well as social learning. Oxytocin present during the perinatal period can tune the central nervous system, potentially supporting adaptive patterns of physiology and behavior in later life. Oxytocin also helps to regulate the autonomic nervous system, with consequences for sensory, visceral, metabolic, and smooth motor systems. Throughout the lifespan oxytocin may increase social sensitivity and modulate reactivity to stressors. Oxytocin can encourage emotional states that allow optimal development and the social use of others during periods of stress and restoration. Oxytocin protects and heals tissues and has therapeutic consequences that are only now being discovered.

The actions of oxytocin are tightly interwoven with a genetically related and structurally similar neuropeptide, vasopressin. Vasopressin influences the functions of oxytocin, and vice versa, in part because these peptides are capable of binding to each other's receptors. In contrast to oxytocin, vasopressin has been associated with mobilization, anxiety, and defensive behaviors, but also the formation of selective social bonds. Interactions between

oxytocin and vasopressin are difficult to study and are not discussed in detail here. However, the dynamic interplay between these two peptides and a host of other molecules, such as dopamine (Aragona & Wang 2009, Young et al. 2011) and endogenous opioids (Burkett et al. 2011), supports social behaviors, especially in the face of challenge.

Characterized initially as a “female reproductive hormone,” it is now clear that oxytocin has effects in both sexes (Lee et al. 2009). Vasopressin may be of particular importance in males but also has functions in females. However, at least some of the effects of these peptides differ between males and females (Carter 2007, Carter et al. 2009a, De Vries & Panciza 2006, Taylor et al. 2010). Sex differences in the actions of oxytocin and vasopressin, especially in early life, may be fundamental to sex differences in behavior, although this is not currently well studied.

Dozens of recent papers have documented the importance of oxytocin, especially in the context of genetic variations. Polymorphisms and epigenetic modification of receptors in the oxytocin pathways contribute to both individual differences in social behavior and the management of challenge across the life cycle. In addition, studies of the effects of intranasal oxytocin are offering a new perspective on the role of oxytocin in human behavior. The importance of oxytocin also is supported by the success of new therapies in which this peptide is used for the treatment of maladaptive social behaviors and physical dysfunctions. Those findings are not described here but are detailed in many excellent reviews, such as those of Ebstein et al. (2012), Feldman (2012), Lee et al. 2009, MacDonald & Feifel (2013), and Meyer-Lindenberg et al. (2011).

THE EVOLVED BIOCHEMISTRY OF SOCIAL BEHAVIOR

The need to interact with others of their own species is not unique to vertebrates. Reliance on others and positive social interactions appeared early and often in the course of evolution. For example, asexual bacteria reproduce more successfully and produce complex biological structures in the presence of others (Ingham & Ben Jacob 2008). Social behavior and the benefits of sociality are considered central to evolution. However, genetic pathways for eusociality, such as the social systems seen in colonies of bees and termites, have evolved several times in insects. In fact, the genetic systems responsible for social behavior

in insects appear to reflect the actions of an “accelerated” form of evolution (Woodard et al. 2011).

Social behaviors are likely to have multiple genetic and physiological origins and substrates. Thus, whether a common genetic core underlies the tendency toward sociality across or among vertebrates and invertebrates remains to be determined. Even in nematodes, oxytocin-like molecules regulate a series of interactive behaviors and social interactions necessary for successful mating (Garrison et al. 2012). The patterns of peptide-stimulated behaviors described in nematodes appear to be strikingly similar to those seen in vertebrates. Furthermore, the subcellular signaling properties of the class of molecules to which oxytocin belongs are associated with behavioral phenotypes that are consistent among widely divergent animals (Yamashita & Kitano 2013).

There is strong evidence that a suite of molecules with properties necessary for fundamental functions---such as the regulation of water and minerals, immunity and metabolism---have been repeatedly repurposed for various functions. In multicellular animals, neural and endocrine systems coordinate physiology with the demands of the physical and social environment. The genes responsible for oxytocin-like peptides are believed to have evolved more than 700 million years ago (Donaldson & Young 2008), initially regulating cellular processes, such as water balance and homeostasis, that defend cells from dehydration. In the course of mammalian evolution these versatile molecules acquired a host of new functions, including the regulation of complex social behaviors (Goodson et al. 2012).

The developmental importance of oxytocin must be appreciated in the context of the phylogeny and anatomy of the nervous system. The evolution of mammalian physical traits was concurrent with the evolution of oxytocin and its role in mammalian development. Why or how this occurred is not known. However, unique anatomical changes appear to have accompanied the eventual evolution of the human nervous system, with our exceptionally large neocortex, permitting the capacity for language and human social cognition. Possible roles for oxytocin in the development and expression of the human nervous system are detailed below.

OXYTOCIN PATHWAYS

Physiological and Anatomical Characteristics of the Oxytocin System

Oxytocin is a 9 amino acid peptide hormone composed of a 6 amino acid ring and a 3 amino acid tail. At least some of the functions of oxytocin may be explained by the dynamic biological properties of the sulfur bonds that create the ring in oxytocin and that allow the oxytocin molecule to form temporary and long-lasting unions with other chemical entities (Martin & Carter 2013). The now well-established capacity of oxytocin to play a role in social bonds (Carter et al. 2008) appears to be built upon the chemistry of this remarkable molecule, which itself forms bonds throughout the body.

Oxytocin is not a classical neurotransmitter, i.e., limited to local actions by crossing a synapse between an axon and dendrite for its effects. Rather, oxytocin appears to be released from the neuronal soma, axons, and dendrites, acting broadly in the nervous system as a neuromodulator. Upon release, oxytocin may flow through neural tissue by a process termed volume transmission (Neumann & Landgraf 2012). For example, there is evidence that oxytocin from the paraventricular nucleus (PVN) of the hypothalamus can reach the central amygdala via anatomical “expressways,” allowing this molecule to quickly modulate emotional functions of the amygdala and brain stem (Stoop 2012). In the presence of oxytocin, avoidance or fear may be replaced by approach and positive emotional states (Carter 1998).

The cells that synthesize oxytocin are most concentrated in hypothalamic, midline neurons. In particular the PVN and supraoptic nuclei of the hypothalamus contain large cells expressing high levels of oxytocin, with separate cells expressing vasopressin (Gainer 2012). The exceptionally large magnocellular neurons, which synthesize oxytocin and vasopressin, also extend processes to the posterior pituitary gland.

The PVN is a major site of convergence and integration for neural communication relating to stress, affective disorders, and cardiovascular regulation, with effects on the hypothalamic-pituitary-adrenal (HPA) axis and autonomic function (Herman 2012). Oxytocin is colocalized in a subset of neurons in the PVN with major adaptive or stress hormones, such as corticotropin-releasing hormone (CRH), which regulates the HPA axis and which also has been implicated in some of the detrimental effects of chronic stress (Aguilera et al. 2008). Oxytocin may be co-released with CRH as an adaptive response to a

variety of challenges, both positive and negative (Carter et al. 2008, [Neumann & Landgraf 2012](#)).

Oxytocin can be released in a coordinated fashion, within the brain and at the posterior pituitary, into the general circulation ([Neumann & Landgraf 2012](#)). It is likely that the ability of oxytocin to have exceptionally broad and synchronized behavioral and physiological consequences is related to this capacity for movement throughout the brain and body ([Stoop 2012](#)).

Oxytocin is produced tonically. In typical humans basal levels of oxytocin vary among individuals, but in plasma oxytocin, levels are notably consistent across time ([Dai et al. 2012](#), [Gouin et al. 2010](#), [Weisman et al. 2013](#)). Oxytocin also can be released as pulses, thus promoting muscle contractions in tissues such as the uterus and mammary gland, especially when these tissues are steroid primed.

The pulsatile release of oxytocin neurons may be related to the plasticity of the hypothalamic cells ([Theodosis 2002](#)). In adult rats, oxytocin-synthesizing neurons undergo physical transformations in response to hormonal and social stimulation. During pregnancy, birth, and lactation, and perhaps under other conditions such as dehydration or sexual stimulation ([Carter 1992](#)), glial processes that normally separate the oxytocin-containing neurons are retracted, allowing electrical coupling and then the pulsatile release of oxytocin. Vasopressin-containing neurons typically do not show this form of plasticity and pulsatile release. Furthermore, oxytocin-producing cells are sensitive to oxytocin itself; thus, a form of autocrine feedback regulates the functions of oxytocin-producing cells. Stimulation of the oxytocin system may feed forward to release more oxytocin, and in some cases administration of oxytocin appears to enhance the synthesis of endogenous oxytocin in the central nervous system ([Grippe et al. 2012](#)).

Oxytocin may be available at high levels in blood and brain. The messenger RNA for oxytocin has been reported in rats to be the most abundant transcript in the hypothalamus ([Gautvik et al. 1996](#)), possibly translating into very high concentrations of the oxytocin peptide in the brain. Oxytocin also is found in abundance in blood, as measured by an antibody-based enzyme immunoassay (Carter et al. 2007, [Kramer et al. 2004](#)). It has been suggested that these high levels are measurement artifacts caused by the binding of antibodies to nonhormonal components of blood ([Szeto et al. 2011](#)). However, recent

studies using mass spectrometry, widely accepted as the gold standard for determining peptide levels, support the hypothesis that oxytocin is truly abundant in blood but is sequestered by binding to other molecules in plasma. Thus, measurement methodologies that commonly involve extraction of other molecules in blood, such as albumin, may discard the majority of the oxytocin and greatly underestimate the abundance of oxytocin (Martin & Carter 2013).

Levels of oxytocin in blood and brain vary across species (Kramer et al. 2004). Furthermore, individual differences in oxytocin are common, and these have been related to individual traits, including social behavior (Gouin et al. 2010) and some of the novel patterns of behaviors associated with schizophrenia (Rubin et al. 2011). In Williams syndrome, dramatic individual differences in both oxytocin and social behavior also were detected and are associated with a unique behavioral phenotype (Dai et al. 2012).

Vasopressin: Adaptation and Survival in a Hostile Environment?

Vasopressin is genetically and structurally related to oxytocin, with only two amino acids distinguishing the two molecules. Both oxytocin and vasopressin evolved by duplication from a common ancestral molecule, presumed to be vasotocin (Goodson et al. 2012). Vasopressin's functions may be closer to the more primitive functions of the molecules from which these peptides arose (Albers 2012).

The biological actions of vasopressin, which include water conservation, probably facilitated survival and the transition to terrestrial living, and may have been co-opted across evolution to regulate defensive behaviors and aggression (Ferris 2008, Frank & Landgraf 2008). Vasopressin is critical to social adaptation in a demanding world, with a behavioral profile that is associated with attachment to and defense of self, family, and other members of our social networks (Carter 1998).

For example, vasopressin plays an important role in the selective sociality necessary for pair bond formation (Carter 1998, Winslow et al. 1993). However, many of the functions of vasopressin differ from those of oxytocin (Carter & Porges 2013, Neumann & Landgraf 2012, Stoop 2012). For example, in maternal behavior oxytocin is critical to nursing and important to nurturing (Pedersen 1997), whereas vasopressin has been implicated in maternal aggression (Bosch & Neumann 2012) and paternal defense of the young (Kenkel et al. 2012, 2013). Some aspects of vasopressin's functions within the nervous system are

sexually dimorphic, with possible implications for sex differences in the tendency to show defensive behaviors and for disorders, such as autism, that are male biased (reviewed in [Carter 2007](#), [Carter et al. 2009a](#)).

In the socially monogamous prairie voles, the development of pair bonds is associated with a preference for the familiar partner and other family members, and concurrently the emergence of potentially lethal aggression toward outsiders ([Carter et al. 1995](#)). Either vasopressin or oxytocin can facilitate the general tendency toward social contact in prairie voles. However, in that species both oxytocin and vasopressin appear to be necessary for selective sociality and pair bonding ([Cho et al. 1999](#)) and possibly male parental behavior ([Kenkel et al. 2012](#)). Mate guarding and aggression toward strangers in prairie vole males appear to rely primarily on vasopressin ([Winslow et al. 1993](#)). Thus, the behavioral motif of vasopressin-like molecules is strongly associated with defensiveness and survival ([Albers 2012](#)).

Vasopressin also may synergize with CRH ([Aguilera et al. 2008](#)) to increase stress reactivity, anxiety, and repetitive behaviors, such as territorial marking in rodents ([Ferris 2008](#)). Vasopressin also has been associated with defensive aggression and emotional dysregulation ([Albers 2012](#), [Coccaro et al. 1998](#)). Some of the effects of vasopressin are opposite to those of oxytocin, and both hormones are probably critical for optimal reproduction and survival ([Carter 1998](#), [Carter & Porges 2013](#), [Neumann & Landgraf 2012](#)). However, in general vasopressin is associated with stress and arousal. Because vasopressin is important in defensive behaviors ([Winslow et al. 1993](#)), it also is possible that vasopressin can lower the threshold to aggression ([Ferris 2008](#)).

Vasopressin elevates blood pressure and has been implicated in cardiovascular disease as well as posttraumatic stress disorder (PTSD) ([Wentworth et al. 2013](#)). This peptide is synthesized in brain regions that regulate biological rhythms and may play a role in sleep disturbances and insomnia---perhaps contributing to disorders such as PTSD. It is plausible that oxytocin is protective against PTSD ([Olf 2012](#)), possibly through its capacity to counteract some of the hyperarousal associated with vasopressin.

Sex differences in the management of stressful experiences may be at least partially influenced by vasopressin ([Carter 1998](#), [Taylor et al. 2000](#)). The synthesis of vasopressin is androgen dependent, especially in the medial amygdala and bed nucleus of the stria

terminalis, from which it is released into the lateral septum (DeVries & Panzica 2006). We have speculated that this sexually dimorphic central axis may be of particular relevance to sex differences in male-biased disorders such as autism (Carter 2007).

Receptors for Oxytocin and Vasopressin

Although beyond the scope of this review, it is useful to understand that the functions of oxytocin and vasopressin depend on their capacity to bind to specific receptors. The expression of receptors for oxytocin and vasopressin are modulated by both genetic and epigenetic processes, which are only now becoming apparent (Ebstein et al. 2012, Gregory et al. 2009). Only one oxytocin receptor has been described, the gene for which (*OXTR*) is located on chromosome 3p24--26 (Gimpl & Fahrenholz 2001). The *OXTR* gene encodes a G-protein-coupled receptor with a seven-transmembrane domain. The same oxytocin receptor is present in neural tissue and in other parts of the body, such as the uterus and breast.

Three receptor subtypes have been identified for vasopressin. Of these, the vasopressin receptor 1a (V1a), which is found in the brain, has been associated with social behavior, especially in males, as well as the regulation of responses to stressors, blood pressure, and other cardiovascular functions. The V1b receptor has been implicated in endocrine and behavioral responses to stressors and aggression (Stevenson & Caldwell 2012). The V2 receptor is localized to the kidney and does not appear to be involved in behavior.

Receptors for both oxytocin and vasopressin are abundant in areas of the nervous system that regulate social, emotional, and adaptive behaviors including the amygdala, the HPA axis, and the autonomic nervous system. Both individual and species differences in V1a receptor distributions have been identified. Among the sources of these differences are species-typical genetic variations in the promoter region of the gene for the V1a receptor (Hammock & Young 2005). The oxytocin receptor also shows species differences in expression, which may be of considerable relevance to species differences in social behavior and emotion regulation.

BEHAVIORAL AND NEUROBIOLOGICAL CONSEQUENCES OF OXYTOCIN

Mammalian Reproduction and Parenting Shape the Nervous System

Mammalian behavior is particularly dependent on selective social interactions. Young mammals are supported by the mother or other caretakers during gestation, birth, and the postpartum period (Hrdy 2009). During the prenatal and postpartum periods mammalian offspring are emotionally and physiologically tuned by these caretakers (Feldman 2012). Much of the mammalian neocortex develops postnatally, during a period when offspring are nourished by milk and reliant on maternal behavior and other aspects of group living (Hrdy 2009). In humans the maturation of the neocortex occurs over an exceptionally long period, with some processes extending into the fourth decade of life (Rakic 2009, Somel et al. 2013). Mechanisms that maintain relationships and social support over the lifetime of an individual may be especially important in humans, allowing time for learning a large repertoire of social and cognitive behaviors, and for the acquisition of an extensive social network.

A biological prototype for mammalian sociality, and especially selective social bonds, can be found in the mother--infant interaction and lactation (Carter 1998). Lactation is unique to mammals and relies on oxytocin (among other hormones). The neurobiological substrates for gestation, birth, and lactation allowed the emergence in mammals of an increased brain size. In humans the brain continues to mature well into adulthood (Somel et al. 2013).

Gestation, lactation, and high levels of maternal behavior provide nurture for offspring. The mammalian birth process accommodates the enlarged primate nervous system, while increased parental investment is necessary to nourish and protect the immature offspring and to support the elaboration of the primate nervous system (Keverne 2013). Furthermore, lactation---especially frequent and nocturnal nursing---has the capacity to suppress maternal ovarian function. Whether oxytocin is directly involved in lactational amenorrhea is not well studied, but this is plausible since oxytocin has been directly implicated in ovulation (Niswender et al. 2007). Because lactational suppression of ovulation can be contraceptive, it contributes to spacing births, with indirect consequences for resource allocation. Mothers who are gestating or rearing fewer babies can contribute more to the physical, emotional, and cognitive development of a given offspring. Oxytocin also is present in human milk, which also may serve as a form of social and hormonal communication between mother and baby. The lactating mother, with increased potential to release oxytocin, also has reduced

reactivity to stressors (Carter & Altemus 1997). These adaptations increase maternal behavioral flexibility in the face of the demands of child rearing and also can modify the behavior and physiology of the infant (Zhang & Meaney 2010), with consequences that vary according to environmental demands and with the history of the mother.

Much of the neocortex develops postnatally, during a period when offspring are supported by maternal behavior and milk. Among humans living in foraging societies, other group members play critical roles in caring for and provisioning offspring (Hrdy 2009). Social bonds are especially important to selectively direct social behavior toward familiar others, who are often family members or sexual partners. In turn, cohesion of the family or social group facilitates successful reproduction and fitness, which has been documented in modern nonhuman primates living in nature (Seyfarth & Cheney 2012, 2013).

Maternal oxytocin acts as a signaling mechanism between the mother and fetus). Of particular importance to cortical and hippocampal functioning is gamma-aminobutyric acid (GABA). Maternal oxytocin released during birth triggers a switch in GABA signaling in the fetal brain from excitatory to inhibitory. Inhibitory GABA is necessary for cognitive functions. In vivo administration of an oxytocin antagonist before delivery prevents this switch of GABA activity in fetal neurons and aggravates the severity of hypoxic episodes (Tyzio et al. 2006) . Maternal oxytocin apparently inhibits fetal neurons and concurrently increases their resistance to hypoxia, which can serve to protect cortical tissue during birth. The birth-related surge in oxytocin also helps to regulate the synchronization of the fetal hippocampal neurons, possibly facilitating the transition from prenatal to postnatal life (Crepel et al. 2007, Khazipov et al. 2008). Such changes have long-term consequences for emotional and cognitive functions and the growth of the nervous system.

Placental gestation and live birth are critical to mammalian brain development. The placenta is regulated by the maternal genome, providing an early source of nutrition for the fetus and giving the mother further opportunity to influence the size of her offspring (Keverne 2013). Mice in which the gene for oxytocin or its receptor is genetically disrupted are still capable of birth. However, in primates or other mammals with a large cranium, oxytocin may have a special importance by creating the strong contractions needed to expel the fetus from the uterus. Delivering a large baby, which involves prenatal maternal investment, cervical stimulation, and the release of oxytocin, as well as stress and pain, may

increase the attachment between the mother and offspring. As one example, the success of precocial mammals such as sheep, whose infants must follow the mother immediately following birth, depends on high levels of cortical-motoric maturation as well as selective attachment to the mother, who is the infant's source of food and protection (Keverne 2013). In addition, oxytocin may serve to protect both mother and infant from pain (or from the memory of pain) associated with childbirth (Mazzuca et al. 2011), thus further promoting attachment. Emerging evidence also indicates that maternal oxytocin may protect a mother from postpartum depression (Stuebe et al. 2013).

In socially monogamous or communal species, care of the young often extends beyond the maternal-infant unit (Hrdy 2009). In this context it is useful to note that interacting with an infant can release oxytocin in adult males, including humans (Feldman 2012) and prairie voles (Kenkel et al. 2012). In turn, the release of oxytocin in males by stimuli from the infant could facilitate coping with the complex needs of the infant. For example, when reproductively naive males are exposed to an infant, they quickly enter a physiological state characterized by activation of both the sympathetic and parasympathetic nervous systems. This somewhat novel physiological state, which probably depends on interactions between oxytocin and vasopressin, allows the simultaneous appearance of nurture and protective forms of social behavior (Kenkel et al. 2013).

Oxytocin and Love

Although research is actually rather meager, there has been a popular acceptance of oxytocin as the "hormone of love" (reviewed in Carter & Porges 2013). Nonetheless, within the past decade, research in animals, including humans, has confirmed and extended the general conclusions drawn from research in rodents (Carter 1998).

The initial stages of falling in love with a new partner may include excitement and arousal (Fisher et al. 2006). Oxytocin has been implicated in social attention and eye gaze (Guastella & MacLeod 2012), which often are critical in early stages of relationship formation. The initial stages in a passionate relationship, as well as the experience of sexual arousal and orgasm, could draw upon the apparent capacity of oxytocin, and presumably also vasopressin, to permit increased sympathetic arousal without parasympathetic retraction (Carter 1992, Kenkel et al. 2013, Norman et al. 2011).

Inherent in most definitions of love are social communication, feelings of empathy, and a sense of reciprocal trust. Results from computerized games and other forms of behavioral paradigms have implicated oxytocin in trust (Kosfeld et al. 2005), empathy (Carter et al. 2009b), cooperation (Hurlemann et al. 2010, Rilling et al. 2012) and neural activation in brain regions associated with sociality (Jack et al. 2012). Oxytocin may mediate the buffering effects of positive relationships and modulate reactivity to stressful experiences. In general, oxytocin tends to support a sense of safety and social behaviors characterized by “immobility without fear” (Porges 1998, p. 852). Thus, the capacity to be close to and sensitive to others, which is typical of loving relationships, can be supported by oxytocin’s behavioral effects.

Key to positive relationships between adults are selective social behaviors and social bonds. Studies originally conducted in prairie voles revealed that oxytocin was capable of facilitating social contact as well as selective social preferences in both sexes (Cho et al. 1999, Williams et al. 1994). In prairie voles, mating facilitated the onset of pair bonding (Williams et al. 1992), a behavior that was later shown to be dependent on oxytocin (Williams et al. 1994). In the prairie vole model, access to both oxytocin and vasopressin receptors appears necessary for pair bonding to emerge, whereas either oxytocin or vasopressin alone facilitates nonselective sociality (Cho et al. 1999, Young et al. 2011). Whether human social behavior and attachments can be formed in the absence of oxytocin or vasopressin is not known.

Oxytocin is released in response to a variety of experiences and stimuli and under various circumstances, both positive and negative (Carter 1992, Dai et al. 2012, Feldman 2012). Attachments and social bonds also form under many different kinds of conditions. These and many other studies leave little doubt that oxytocin plays a central role in the social behaviors that lie at the heart of the human experience of love. However, it is likely that vasopressin also plays a major role in emotional and visceral experiences.

Other Emotionally Powerful Social Behaviors

Powerful positive social behaviors and experiences may be built upon the primal functions of oxytocin and vasopressin. For example, social and emotional cohesion appears to be biologically based. In fact, humans are so deeply interwoven with and dependent upon others of our own species that we may fail to recognize the fundamental nature of social

behavior. Hofer (1987), on the basis of his studies of the development of the maternal and infant dyad, concluded that regulators of physiology were embedded in social behavior. Hofer's concept of "hidden regulators" focused on the benefits of proximity. However, other forms of interaction, including those encoded as cognitive experiences, can mediate human behavior. The importance of hidden regulators to emotional states of course is not limited to mothers and infants.

Humans gain pleasure from working together. We share the emotions of others and can experience emotional contagion (Hatfield et al. 1994). We experience emotional elation from playing team sports and from observing the triumphs of others (Pepping & Timmermans 2012). Experiencing the physical and emotional consequences of the feelings of others may encourage humans to emulate the virtuous behavior of others, including the expression of positive social behaviors and social cohesion (Koh & Fredrickson 2010).

Healthy humans are more capable than other apes of vicariously experiencing and responding to the emotional states and experiences of others. Studies of empathy have often focused on negative emotional states or the pain of others (Decety 2011). However, it is also possible to measure behavioral and neural changes as a function of "witnessing acts of moral beauty" in others---a process that has been termed moral elevation (Englander et al. 2012, p. 1). Experiencing "other praising emotions," including admiration, gratitude, and elevation, can be accompanied by a novel set of experiences and emotional responses, which are differentiated experimentally from more conventional positive emotions such as joy and amusement (Algoe & Haidt 2009). Hints regarding the biological basis of moral elevation come from the phenomenology of this behavior, which includes autonomic shifts such as chills or tearing.

Moral elevation has a particularly interesting effect on the nervous system as measured by neural imaging. Neural synchronization (within a subject) of midline brain regions occurred during videos known to elicit moral elevation (Englander et al. 2012). Among the brain regions activated by moral-elevation videos were the medial prefrontal cortex and insula. These same brain areas have been implicated in self-referential and interoceptive processes and may regulate autonomic responses. Synchrony in these brain regions did not consistently occur during videos depicting admiration or neutral (i.e., nonemotional) stimuli. It is likely that highly emotional responses, including moral elevation, are supported

by a common underlying neurophysiology---possibly including those responses associated with falling in love. Oxytocin has been implicated in moral elevation by the fact that lactating women express milk during elevating experiences (Silvers & Haidt 2008). However, whether this is cause or effect, or both, is not known.

Positive experiences also can change pain thresholds, possibly in part through actions of oxytocin. For example, social laughter can raise pain thresholds (Dunbar et al. 2012). In the latter study, reduced sensitivity to pain during social laughter was attributed to possible changes in endogenous opioids, although biochemical measures of opioids (or oxytocin) were not taken. However, in other human experiences, including birth, lactation (Brunton & Russell 2010), and early development (Mazzuca et al. 2011), oxytocin has been implicated in both pain regulation and events that may create pain. Oxytocin dynamically interacts with endogenous opioids (Burkett et al. 2011), and this interaction has broad implications for human behavior.

Oxytocin and Coping with the Stress of Life

Oxytocin is a component of the capacity of the mammalian body to manage the response to challenge. Animal research suggests that acute stressors, especially of high intensity, can release oxytocin in both sexes (Neumann & Landgraf 2012, Pournajafi-Nazarloo et al. 2013). In the face of a severe challenge, oxytocin could initially support an increase in arousal and activation of the sympathetic nervous system and other components of the HPA system. A large pulse of oxytocin also might activate vasopressin receptors, further supporting mobilization and potentially defensive responses. The arousal-enhancing effects of oxytocin, and presumably the release of oxytocin, may differ widely among individuals and are likely influenced by social history and context (Bartz et al. 2011).

In the face of chronic stress, the anti-stress effects of oxytocin may take precedence, permitting a more passive form of coping and immobility without fear (Porges 1998). In addition, sex differences are commonly observed in the capacity of oxytocin or vasopressin to influence stress management. Oxytocin appears to be a component of a more social or passive coping strategy, whereas vasopressin may permit active and mobilized coping strategies (reviewed in Carter 2007; Taylor et al. 2000, 2010).

Behavioral, physiological, and anatomic data from rodents (Kenkel et al. 2013) and humans (Grewen & Light 2011) suggest that the antistress effects of chronic oxytocin

downregulate the sympathetic nervous system while supporting the protective and restorative functions of the vagal systems.

As one behavioral example, individuals with higher levels of parasympathetic activity showed more rapid increases in self-described positive emotions and a sense of connectedness (Koh & Fredrickson 2010). These and other findings suggest that oxytocin has effects on the regulation of emotion, the mammalian autonomic nervous system, homeostasis, coping, and healing, helping to explain the important consequences of the presence or absence of social engagement and attachment. Oxytocin and social support have been implicated in human wound healing (Gouin et al. 2010) and are protective against cardiovascular dysfunction. Oxytocin may act to protect or repair tissue (Karelina & DeVries 2011). Oxytocin also has antioxidant and anti-inflammatory properties across the lifespan and even in tissue models in vitro (Gutkowska & Jankowski 2012, Szeto et al. 2008). These adaptive properties of oxytocin further help to explain the capacity of loving relationships and psychological safety to protect and heal in the face of stress and adversity.

The Effects of Oxytocin Treatments Are Not Always Prosocial

Recent human research, particularly studies conducted in individuals with a history of personal adversity, suggest that in some contexts exogenous oxytocin can have asocial or negative consequences (Bartz et al. 2011), including increasing the perception of threat in the presence of individuals from other social groups (De Dreu 2012). There is recent evidence from studies in mice that oxytocin, through localized actions on the oxytocin receptor, can enhance fear conditioning (Guzman et al. 2013). In some cases negative effects of oxytocin, especially when seen following exogenous oxytocin treatments, could reflect in part the capacity of oxytocin, especially at high doses, to dynamically interact with the vasopressin receptor. In large amounts, oxytocin may stimulate the vasopressin receptor, functioning like vasopressin and enhancing defensive or aggressive responses (see the previous discussion on this point). Aggressive or defensive responses to out-group members are consistent with the behavioral effects of vasopressin found in male prairie voles (Winslow et al. 1993).

It is also possible that the actions of oxytocin differ depending on activity in other neuroendocrine systems, such as those regulated by sex steroids, opioids, catecholamines, or inflammatory cytokines. Support for this notion comes from studies of the factors that

regulate oxytocin during birth (Brunton & Russell 2010) and the prevalence of sex differences emerging from the literature on the actions of oxytocin in humans and other mammals (Carter 2007; Taylor et al. 2000, 2010).

Another example of the apparently paradoxical effects of high levels of oxytocin is seen in Williams syndrome (Dai et al. 2012). This genetic condition, caused by deletion of ~28 genes, is associated with a behavioral phenotype that includes high levels of gregariousness and a tendency to approach strangers but also high levels of anxiety in nonsocial contexts. Endogenous oxytocin, as well as vasopressin, measured in blood varies widely between individuals with this condition. Oxytocin levels were correlated positively with approach to strangers, but high levels of oxytocin also were associated with maladaptive social behaviors in everyday life, in part because individuals with Williams syndrome can be too trusting. Whether this atypical behavioral phenotype can be directly attributed to oxytocin, vasopressin, or---more likely---interactions between these peptides, remains to be determined.

There also is increasing evidence that the effects of exposure to exogenous oxytocin are not necessarily associated with increases in positive sociality. In prairie voles a single low-dose oxytocin injection given on the first day of life facilitated pair-bond formation in adulthood. However, high doses of oxytocin had the opposite consequences, producing animals that preferred an unfamiliar partner (Bales et al. 2007b).. Repeated exposure to oxytocin early in life in pigs also disrupted subsequent social behavior, under some conditions producing piglets that were less capable than normal animals of appropriate and reciprocal social interactions (Rault et al. 2013). Oxytocin given intranasally to prairie voles during adolescence also did not reliably facilitate social behavior and, once again, at some doses disrupted the tendency of this species to show a partner preference (Bales et al. 2013). It is possible that effects such as these also might represent interactions between systems that rely on both oxytocin and vasopressin.

Consequences of Isolation May Be Mediated Through Oxytocin

In the context of the shared physiology among social and emotional behaviors, it is not surprising that social interactions and isolation have powerful physiological consequences. Individuals with a perceived sense of social support are more likely to avoid or survive

illness and have longer lives than otherwise similar people who live alone, especially those who experience a sense of loneliness (Cacioppo et al. 2006).

Experiments in animals provide an opportunity to examine in more depth the physiological consequences of the absence of a social partner. Highly social mammals, including prairie voles, offer useful models for examining the biology of social separation and isolation because they share with humans the capacity to form long-lasting social relationships (Carter et al. 1995). Prairie voles also have a human-like autonomic nervous system, with high levels of parasympathetic vagal activity and a dependence on social behavior for emotion regulation (Grippe et al. 2007, 2009). Because the autonomic nervous system mediates many of the consequences of social interactions (Kenkel et al. 2013), the response of prairie voles to their social environment offers a rodent model for examining mechanisms through which peptides, including oxytocin, regulate reactions to the social environment.

As one example, in prairie voles isolation from a partner for a few weeks produced significant increases in several behavioral measures of depression and anxiety. Isolated animals were less exploratory, showed increases in anhedonia (indexed by a loss of preference for sweet liquids), and were more likely to show immobility in response to a stressor---in this case possibly immobility with fear. (Porges, 1998). In prairie voles, separation from a partner, followed by prolonged isolation, is associated with increases in heart rate, decreases in parasympathetic function, and increases in behavioral reactivity to stressors, such as the presence of a social intruder. Following a 5-minute social stressor (an intruder), isolated prairie voles required an average of more than 15 hours for heart rate to return to baseline. In contrast, animals living in sibling pairs required about 2.5 hours for their heart rate to recover. In the absence of a social partner, oxytocin increased in female (but not male) prairie voles (Grippe et al. 2007). Elevated oxytocin may be protective against the negative consequences of isolation, which include reductions in the expression of the oxytocin receptor (Pournajafi-Nazarloo et al. 2013). However, these findings in voles suggest a possible hormonal advantage for females---at least in comparison to males---in the capacity to cope with isolation. Experiments with female voles revealed that oxytocin injections over a period of weeks were capable of reversing the cardiac and behavioral

effects of isolation, including protecting against the increases in heart rate and reductions in vagal tone that typically accompany isolation (Grippe et al. 2009).

In postmenopausal women, increases in oxytocin also have been associated with gaps in social relationships (Taylor et al. 2006). Releasing oxytocin may be a component of a self-regulatory process that helps mammals deal with isolation or other stressful experiences. These hormonal responses also might facilitate social engagement or relationships, functions that could be especially adaptive in females who under some circumstances may be less able than males to live alone (Taylor et al. 2010). However, it cannot be assumed that males and females use oxytocin pathways in identical ways. Research on the functions of oxytocin and vasopressin in emotional responses and coping holds promise for understanding sex differences in social behavior in a more general sense.

ANATOMICAL, PHYSIOLOGICAL, AND GENETIC EFFECTS OF OXYTOCIN

Genetic and Epigenetic Variation

Oxytocin pathways are influenced by genetic variations and may be epigenetically tuned by social experiences and exposure to hormones. For example, mounting evidence indicates that genetic and epigenetic variations in the *OXTR* gene can predict individual differences in behavior, physiology, and even brain anatomy (Ebstein et al. 2012, Meyer-Lindenberg et al. 2010, Tost et al. 2010). Genetic variations in the *OXTR* gene, indexed by single-nucleotide polymorphisms, were originally related to autism spectrum disorders (variant rs2254298 G>A) (Jacob et al. 2007). Another variant (rs53676 G>A) has been associated with behavior and brain activity in the context of social cues (Ebstein et al. 2012). Studies of this kind are leading to a new awareness of the behavioral importance of oxytocin pathways.

The *OXTR* gene can be silenced via DNA methylation, thus reducing the expression of the oxytocin receptor. Functional relationships between methylation of the *OXTR* gene and behavior have been detected in autism (Gregory et al. 2009). However, within a population with autistic traits, those individuals with the highest levels of methylation were the least behaviorally impaired (S. Jacob & J. Connelly, personal communication). Thus, in at least some cases, methylation of the *OXTR* gene has been associated with beneficial consequences. In humans, methylation status of the *OXTR* gene also has been shown to predict neural responses to ambiguous social stimuli (Jack et al. 2012). Additional research

is needed, but these findings suggest that epigenetic methylation of the *OXTR* gene may be one component of an adaptive strategy, possibly downregulating the oxytocin receptor but also encouraging, through negative feedback, upregulation of the synthesis of the oxytocin peptide.

Oxytocin pathways may be particularly susceptible to modification in early life. It is well established that neonatal social experiences and exposure to hormones can have lifelong consequences for behavior (Carter et al. 2009a). Both social experiences and exposure to the oxytocin peptide around the time of birth appear to epigenetically tune the expression of the oxytocin receptor.

Data from both behavior and measures of peptide receptors suggest that a single exposure to exogenous oxytocin in early life may be capable of producing dose-dependent changes in behavior in adulthood (Carter et al. 2009a). Low---but not high---doses of exogenous hormone facilitated pair bonding as well as the expression of endogenous oxytocin (Bales et al. 2007b). Low doses of oxytocin in early life also inhibited the expression of the V1areceptor in adulthood (Bales et al. 2007a). The enduring consequences of these treatments may reflect the capacity of early exposure to oxytocin to epigenetically regulate the *OXTR* gene.

Oxytocin and the Development of the Human Neocortex

The primate nervous system developed across the course of evolution, with physical adaptations that were critical to permit human behavior, including cognition and speech. It is possible that the diverse physiological mechanisms of action of oxytocin allowed the elaboration of the human nervous system. The role of oxytocin in this process is poorly understood but may be approximated by understanding certain features of the development and evolution of the cortex.

The human brain is two to three times larger than that of related primates, including chimpanzees (Keverne 2013, Somel et al. 2013). This difference is due primarily to increases in cortical tissue, especially neurons located in association areas such as the prefrontal cortex. Creating a physiological and anatomical environment that allowed the extreme encephalization seen in humans appears to have drawn on several of the novel properties of oxytocin.

The origins of the neocortex have been traced to the reptilian ancestor of early mammals and depend on delicately balanced developmental processes (Rakic 2009). During development the cells of the neocortex differentiate, migrate, enlarge, and in some cases undergo cell death (including apoptosis). The human neocortex originates from progenitor cells in the ventricular and subventricular zones of the embryonic brain. Following paths laid by transient radial glia, neuronal cells that will become the neocortex migrate toward the surface of the brain, in most cases bypassing earlier cells. The result is formation of the distinct cytoarchitectural layers of the laminar neocortex permitting specialization of the brain for functions including speech and complex cognitions. Differences in the abundance of progenitor cells between mice and primates can be detected prior to the differentiation of the cortex. For example, it has been estimated by Rakic (2009, p. 726) that fewer than “7 extra rounds of cell division in the progenitor cells at an early embryonic stage would be sufficient to create the 1,000 fold difference in total cortical surface area that differentiates the brains of mice from those of humans.” Thus, initially subtle developmental events may have allowed the eventual evolution of the human neocortex.

Oxytocin, Encephalization, and Social Behavior

Oxytocin encourages encephalization and cognition indirectly through social behavior. Neuroendocrine events, including those that were dependent on oxytocin, apparently support the prolongation of infant care and slow maturation of the human nervous system. This provides humans with an extended period for social learning, the development of an extended network of selective relationships, and cultural intelligence. Species differences in mammalian brain size among primates have been related to the appearance of social bonding, and it has been proposed that social relationships and bonds supported the evolution of the cortex (Dunbar 2009, Seyfarth & Cheney 2012, Shultz & Dunbar 2010). Social support within and beyond the family also may have permitted the evolution of human intelligence (Hrdy 2009). Furthermore, it has been proposed by anatomists that the human nervous system is a product of adaptations for sociality (Adolphs 2009). Perhaps these relationships are regulated in part by differences in the availability of oxytocin or variations in other components of the oxytocin pathways.

Oxytocin May Directly Foster Encephalization

Oxytocin has the capacity to remodel the bodily tissues. Oxytocin can influence cellular growth, death or motility, inflammation, or differentiation, although the most complete work in this area has been done in the heart (Gutkowska & Jankowski 2012). In rodents, apoptosis in heart tissue can be inhibited by oxytocin and especially by the precursor or “fetal” form of oxytocin.

Emerging evidence indicates that oxytocin also has direct effects on brain development. Oxytocin has been shown to reduce apoptosis and to promote adult neurogenesis (Leuner et al. 2012). Systematic analyses of the role of oxytocin in neocortical development are lacking. However, it is plausible that variations in oxytocin might facilitate neocortical growth by encouraging undifferentiated stem cells to grow into cortical cells (Gutkowska & Jankowski 2012) or by inhibiting the programmed destruction of brain cells. Together these processes would synchronize neocortical development to the physical demands of mammalian reproduction. Furthermore, it has been shown in tissue slices from rats that the synchronous firing of cortical cells is facilitated in the presence of oxytocin acting via effects on the GABA system (Crepel et al. 2007). Thus, both the anatomy and functional physiology of the developing mammalian brain could be sculpted by changes in oxytocin pathways.

Oxytocin, Oxygen, and the Growth of the Neocortex

In the transition from reptiles to mammals, and especially to primates, sophisticated autonomic systems emerged that are capable of concurrently supporting social behavior and the physiological demands of the expanding and oxygen-hungry mammalian cortex (Porges 2011). Cortical function is serviced by autonomic processes that originate in the brain stem. The role of the brain stem in cortical function is easily detected. When oxygen is no longer available, following damage to the brain stem or autonomic nervous system, consciousness is lost, typically followed by death. However, under normal conditions the entire brain, including cortical, subcortical, and autonomic pathways, is necessary to coordinate dynamic social behaviors, such as social cognition and social communication, with basic bodily functions, including survival and reproduction.

Critical to primate social engagement and communication are the bones, muscles, and nerves of the face and head, including the larynx, pharynx, and middle ear (Porges 2011). These structures and the nerves that innervate them form a system that permits social

engagement and communication. The muscles of the mammalian face and head also are regulated in part by the autonomic nervous system, which in turn is influenced by oxytocin (Grippio et al. 2009, Quintana et al. 2013). Therefore it is not surprising that functions of the face, such as facial emotions and eye gaze, can be influenced by oxytocin. (Guastella & MacLeod 2012).

The autonomic effects of oxytocin are context dependent and are not simple (Porges 2011). However, growing evidence suggests that oxytocin regulates both sympathetic and vagal branches of the autonomic nervous system (Kenkel et al. 2013). The PVN is a major regulatory center for autonomic functions (Herman 2012). The PVN of the hypothalamus synthesizes oxytocin but also responds to oxytocin. Lower brain stem structures, such as the dorsal motor nucleus of the vagus, also have high concentrations of oxytocin receptors. In addition, most---if not all---of the visceral target organs of the autonomic nervous system, such as the heart and digestive and immune systems, contain receptors for oxytocin and may also locally synthesize oxytocin (Gimpl & Fahrenholz 2001, Welch et al. 2009).

Developmental factors that regulate the capacity of the brain and skull to expand also are indirect determinants of human behavior (Porges 2011). The face and head arise embryologically from ancient gill arches. The detachment from the skull of the middle-ear bones occurred in the evolutionary transition from reptiles to mammals. It is detached middle-ear bones that are used to detect high-frequency sounds, and these bones also provide the definitive fossil evidence that a given species is a mammal (Manley 2010). The developmental and evolutionary detachment of the middle-ear bones also allowed the expansion and elaboration of the face, skull, and neocortex. A possible direct role for oxytocin in skull development has not to our knowledge been reported. However, oxytocin receptors are found in bone, and oxytocin has been implicated in bone growth and remodeling of other bony structures. In fact, oxytocin levels tend to be low in osteoporosis, possibly contributing to the loss of bone flexibility with age (Breuil et al. 2011). Cellular functions of oxytocin often involve the regulation of calcium. Therefore, it is plausible, but not proven, that oxytocin plays a role in the structure of the mammalian skull, helping to make room for the expansion of the human neocortex.

Oxytocin: The War Between the Sexes and Cortical Growth

Live birth puts restrictions on the physical size of an infant, especially the head. A large baby with an expanded neocortex is a physical burden for the mother. In primates, infants are gestated, nursed, and carried for months or years. Reproductive restrictions are further increased in bipedal primates, since mothers must give birth through a pelvic girdle adapted for upright locomotion. Thus, the capacity of the mother to regulate offspring development, especially the size of the neocortex, could be critical to both her survival and reproductive success (Keverne 2013). At the same time, the father's genome may be better served by larger offspring. As originally proposed by Haig (2011), this asymmetrical parental regulation of fetal growth creates a genetic war between the sexes. The weapons for this war include dueling genes and hormones that regulate the growth of the fetal neocortex and skull. Oxytocin is likely to be one of those hormones.

Through a process known as genomic imprinting, the expression of a subset of genes that are of particular relevance to growth and development can be epigenetically determined by one parent versus the other. This is accomplished by selective silencing of one of a pair of alleles for a given gene, allowing the other allele to dominate. Research in mice by Keverne (2013) and his associates showed that the matrilinear germ line contains cells that will become the neocortex, whereas progenitor cells that will become the hypothalamus originate in the father's genome. The primary source of oxytocin is from the hypothalamus, in neurons that are regulated by paternally expressed genes that are susceptible to genomic imprinting.

One paternally expressed gene, known as Peg3, plays a critical role in the development of the hypothalamus as well as the placenta (Broad et al. 2009, Champagne et al. 2009). Evidence for the importance of the Peg3 protein comes from experiments in which the Peg3 gene was inactivated. In the absence of Peg3 gene expression, females had a reduced number of hypothalamic oxytocin neurons, lower reproductive success, and specific reductions in the growth of the offspring that survived. Peg3-gene mutant mothers also were less attentive to their young, showing increased indications of anxiety and aggression (Keverne 2013). Thus, at least in mice, a single gene, the expression of which can be genetically influenced by the father and epigenetically regulated by the mother, has a major role in the synthesis of oxytocin.

Genomic imprinting or epigenetic silencing of the paternal allele of the *Peg3* gene allows the maternal genome to dominate the development of the fetus. Although the genes that produce cells synthesizing oxytocin may originate in the father, it is the mother who determines the expression of these genes and thus the size of her offspring at birth.

At the same time, the mother also assumes the burden of providing food and nurture to her offspring, regulating continued cortical development in what can be an extended postnatal period. Oxytocin also has been implicated in food intake and metabolic efficiency (Chaves et al. 2013). Thus, the maternal endocrine environment affects and potentially “programs” the morphology of her offspring.

A long period of dependence on the mother (or other caretakers) characterizes most primates, especially humans. The slow maturation of the nervous system, possibly paced by the maternal genome, also increases the developmental significance of selective social interactions and long-term attachments. The capacity of a mother (or other caretakers) to maintain a lasting attachment to an offspring is essential to permit the full expression of the traits associated with human sociality and human cognition. As mentioned above, lactation, maternal behavior, and social bonding are functions that rely on oxytocin. If the processes observed in mice apply to humans, then it may be the mother who regulates the timing and eventually the extent of the cortical and bodily development of her offspring as well as the availability of hypothalamic oxytocin. Each of these would have lasting consequences for brain function and behavior.

SUMMARY

Oxytocin is a powerful molecule with a unique and unusually broad profile of biological and behavioral effects. The receptors and tissues upon which oxytocin acts are ancient and have evolved many functions (Ebstein et al. 2012, Garrison 2012, Meyer-Lindenberg et al. 2011, Yamashita & Kitano 2013). Understanding this system provides a window into the evolution and epigenetics of the human brain (Keverne 2013).

Abundant evidence indicates that individual differences in experience, with effects on health and behavior across the lifecycle, are shaped by caretaker-offspring interactions (Zhang & Meaney 2010). The nervous system seems to be especially sensitive in early life to the presence or absence of peptides, such as oxytocin (Carter et al. 2009a) and

vasopressin (Stribley & Carter 1999, Zhang et al. 2012), with epigenetic consequences that may help to explain individual differences in behavior and coping strategies. Although beyond the scope of this review, there is now little doubt of the epigenetic importance of oxytocin and vasopressin (Carter et al. 2009a). Thus, medical manipulations or even rearing procedures that may influence these hormones, especially in early life, should be applied with caution (Harris & Carter 2013).

Throughout vertebrate evolution, the effects of oxytocin-like molecules have been integral to survival and reproduction. In modern humans, the functions of oxytocin facilitate birth and both directly and indirectly influence brain anatomy, allowing the elaboration of the human neocortex and thus cognition and language. The mammalian brain and body are physically remodeled by the presence of oxytocin. Oxytocin plays a role in sensory, autonomic, integrative, visceral, and motor systems. It helps to tune the emotional nervous system in early life. Oxytocin may help to provide a sense of safety or trust. Oxytocin protects and directly heals tissue, with therapeutic consequences that are only now being discovered. Simply put, I suggest here that *Homo sapiens*, with their high level of dependence on social behavior and cognition, could not have evolved without oxytocin.

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