THE ROLE OF OXYTOCIN AND VASOPRESSIN IN ATTACHMENT

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Abstract: Selective relationships and attachments are central to human health and well-being, both in current societies and during the course of evolution. The presence or absence of social bonds has consequences across the lifespan. The neurobiology of attachment is grounded in neuroendocrine substrates that are shared with reproduction and survival. Experimental studies of species, such as sheep or prairie voles, capable of showing selective social behaviors toward offspring or partners, have provided empirical evidence for the role of oxytocin and vasopressin in the formation of selective attachments. Developmental exposure to social experiences and to peptides, including oxytocin and vasopressin, also can "retune" the nervous system, altering thresholds for sociality, emotion regulation, and aggression. Without oxytocin and without the ability to form attachments the human brain as we know it could not exist. Knowledge of the neurobiology of attachment, and especially the role of oxytocin, also has implications for understanding both healthy behavior and treating mental disorders.

Keywords: oxytocin, vasopressin, attachment, love, sex differences

WHAT IS ATTACHMENT?

Humans are highly social mammals, immersed in networks of connections with others including the collaborative creation of families, cultures, and civilizations. Social behaviors range from the tendency to be generally gregarious to selective forms of sociality. Embedded

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in these complex interactions are selective social behaviors and lasting relationships, here termed social bonds or attachments.

Social bonds and attachments are hypothetical constructs. No one has ever directly measured a social bond. Attachments are not easily described or defined. The scientific use of "attachment" and "bonding" has varied across disciplines, creating additional confusion (Carter et al., 2006). Biologists working with animal models have tended to use the terms attachment and bonding interchangeably. However, in psychology strict definitions of attachment arose focused on the relationship of infants and their mothers (Bowlby, 1969).

Definitions of attachment and bonding are inferred indirectly from behavioral and physiological changes (Table 1). In general, social bonds in both human and animal research are defined by selective patterns of response to others (Carter & Keverne, 2017). Social bonds and attachments are often characterized by physical contact or cognitive attraction toward a preferred partner, and in some cases by distress or vocalization in the absence of the partner. Changes in physiological measures, including autonomic, endocrine, or immune changes, also may be used to indirectly index selective social relationships.

THE CONSEQUENCES OF ATTACHMENT

Attachments are most often described in terms of their consequences, which may extend to all aspects of behavior and across the lifespan. Like other mammals, humans rely on positive social interactions for both safety and reproduction. The presence or absence of social relationships has profound effects on a sense of safety, as well as individual survival, reproduction, and eventually genetic survival.

Positive attachments have documented health benefits, and the absence of social bonds can be associated with both physical and mental illness (Cacioppo, Hughes, Waite, Hawkley, & Thisted, 2006). Understanding the mechanisms for the formation of attachment and the benefits of attachments, and other forms of social support, provides important insights into processes that are protective for mental and physical health.

It has been argued that social behavior is a driving force in the evolution of human nature. The biological systems that are necessary for attachments predate human cognition. Attachments, often with multiple caretakers, facilitate the extended periods of nurture necessary for the emergence and optimization of human intellectual development and social development (Hrdy, 2009). The tendency to form selective pair

Table 1. Common Methods for Assessing Attachment

Partner preferences: Selective proximity, physical contact, eye contact
Aggression in defense of the partner
Autonomic, immune, or endocrine responses specific to the presence or absence of the partner
Behavioral distress (crying, agitation, anxiety) in the absence of the partner, usually resolving in the presence of the partner
Brain-region specific changes in function indexed by
Intermediate early genes (c-fos expression)
Functional imaging (fMRI - BOLD changes or DTI)
Gene expression, specific to putative peptides or related neurotransmitters
Receptor-specific changes in gene expression

bonds, or other kinds of social attachments, is a universal human characteristic (Fisher, 2016).

THE HORMONAL BASIS OF ATTACHMENT

At least some of the benefits of attachments may be attributed to physiological processes supported by specific chemical pathways including those that involve two neuropeptides, oxytocin and vasopressin. Oxytocin and vasopressin are genetically and structurally related with only two amino acids distinguishing the two molecules. Both evolved from a common ancestral molecule, presumed to be vasotocin (Goodson & Kingsbury, 2013).

Neither oxytocin nor vasopressin is a classical neurotransmitter, limited to local action across a synapse. Rather, these molecules appear to be released from the neuronal soma, axons, and dendrites, acting broadly in the nervous system as neuromodulators. The cells that synthesize oxytocin are most concentrated in the hypothalamus, in particular the paraventicular nucleus (PVN) and supraoptic nuclei (SON); in these nuclei separate cells generally express oxytocin and vasopressin.

There is evidence that oxytocin from the PVN can reach the central amygdala via neuronal pathways and possibly also "expressways" allowing this molecule to quickly modulate emotional functions of the amygdala and brain stem (Stoop, Hegoburu, & van den Burg, 2015). Oxytocin can thus be released in a coordinated fashion within the brain and at the posterior pituitary and then into the general circulation (Grinevich, Knobloch-Bollmann, Eliava, Burnelli, & Chini, 2016). 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, as well as the location of receptors throughout the body (Gobrogge, Jia, Liu, Wang, 2017).

Oxytocin is thus part of a dynamic system that, in a context of safety, allows the optimal expression of positive social behaviors including the selective "sociality" that characterizes social bonds. There are several mechanisms through which oxytocin may affect behavior (Table 2). Oxytocin has been implicated in social engagement and eye gaze (Quintana, Alvares, Hickie, & Guastella, 2015), which are critical in early stages of social engagement and relationship formation.

In healthy people, oxytocin seems to serve as a biological and emotional indicator of safety. Oxytocin supports emotional and autonomic processes allowing for what Porges described as "immobility without fear" (2011). In one sense this has to do with oxytocin's action on brainstem receptors, which can increase parasympathetic influences via vagal pathways and oxytocin's capacity to dampen the mobilization and defensive circuits supported by the sympathetic nervous system. "Immobility without fear" in this context is an important biobehavioral enabler providing opportunities to express attachment—it represents a "neural choice" to stay in one place. "Staying in one place" may have been an evolutionary precursor to "falling in love"—another form of attachment that is influenced by oxytocin (Carter, 1998).

In a variety of experiments oxytocin has been implicated in both the causes and consequences of attachment (Bernaets et al., 2017). Oxytocin, administered as an intranasal spray, has been shown to enhance the processing of social information and can facilitate a sense of trust or empathy (Feldman, 2017; Quintana, Alvares, Hickie, & Guastella, 2015). Oxytocin may mediate the buffering effects of social support, and modulate anxiety and over-reactivity to stressful experiences (Carter, 1998; Neumann & Slattery, 2016).

In general, oxytocin tends to support a sense of safety and social behaviors. These and other findings suggest that oxytocin has effects on the regulation of emotion, the mammalian autonomic nervous system, homeostasis, coping, and healing; functioning together these help to explain the important consequences of the presence or absence of social engagement and attachment. 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.

Table 2. Oxytocin and Vasopressin May Influence Social Bonding via Peptide Variations

Relative abundance in brain (or measured in bodily fluids)
Differential molecular forms (e.g., mature 9 amino acid forms vs. precursors)
Selective release (in presence of a preferred partner)
Selective localization (brain-region or cell-type specific)
Co-localization with other molecules (tissue and cell-type specific; e.g., oxytocin and dopamine, or oxytocin and CRH)
Peptide receptors (region-specific variation or sensitivity)
Abundance in specific brain areas (e.g., nucleus accumbens)
Proxy tissues for noninvasive measurement (e.g., white blood cells)
Behaviorally relevant differences in sensitivity or changes in Peptides or Receptors
Species (genetic variation)
Gender (genetic and epigenetic variation)
Individual differences in genetics or epigenetics (including sensitivity)
(e.g., single-nucleotide polymorphisms; SNPs)
(e.g., methylation based silencing of genes regulating function)
(e.g., intergeneration changes)
Differential experiences and adaptive changes, especially during periods of sensitivity including:
Prenatal (e.g., stress, disease, maternal diet, drugs, etc.)
Birth (e.g., naturally occurring variation and/or birth interventions)
Postnatal (e.g., maternal care, stress, disease, diet, drugs, etc.)
Adolescence (e.g., forming new relationships, disease, diet, drugs, etc.)
Aging (e.g., loss of long-term partners, disease, diet, drugs, etc.)

VASOPRESSIN AND OXYTOCIN ARE BOTH COMPONENTS OF AN INTEGRATED SYSTEM REGULATING SOCIAL BEHAVIOR

Oxytocin does not act alone and many of its effects are regulated by interactions with vasopressin. Vasopressin and oxytocin are functionally part of, and thus may be considered, one pathway. Both hormones are responsive to environmental and social demands, although in somewhat different ways (Carter, 1998, 2014; Neumann & Slattery, 2016). Oxytocin acting alone appears to be a component of a more social or passive coping strategy, whereas vasopressin may permit active and mobilized coping strategies (Carter, 1998, 2007).

Both oxytocin and vasopressin are necessary for the expression of selective social behaviors (Cho, DeVries, Williams, & Carter, 1999; Tabbaa, Paedae, Liu, & Wang, 2016), sexual behavior (Albers, 2015; Carter, 1992), and protection of offspring, whether that be maternal or paternal (Bosch & Neumann, 2012; Kenkel, Perkeybile, & Carter, 2017). Act-

ing together oxytocin and vasopressin appear to support autonomic and emotional peak experiences such as falling in love, orgasm, and dealing with an initial exposure to a baby (Carter, 1992; Kenkel et al., 2012, 2013). The early stages in various passionate relationships, as well as the experience of sexual arousal and orgasm, could draw upon the capacity of oxytocin and vasopressin to permit increased sympathetic arousal without parasympathetic retraction (Carter, 1992; Kenkel et al., 2013; Norman et al., 2011).

The functions of oxytocin and vasopressin depend on their capacity to bind to a set of specific receptors. 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 (Gobrogge, Jia, Liu, & Wang, 2017; Stoop, Hegoburu, & van den Burg, 2015).

At the core of attachment are neurobiological systems that regulate fear and threats and those that regulate a sense of security. While oxytocin may activate the more "passive" aspects of attachment, vasopressin activates the more possessive, and in some cases more aggressive side of attachment. Activation of vasopressin receptors is essential for the more protective behaviors, often associated with pair bonds, especially—but not exclusively—in males (Winslow, Hastings, Carter, Harbaugh, & Insel, 1993). Animal research using receptor-specific blocking agents suggests that activation or blocking of vasopressin receptors helps to explain the complex behavioral consequences of oxytocin and vasopressin (Albers, 2015). For example, in hamsters exogenous oxytocin can increase measures of aggression, but these effects were no longer apparent if the vasopressin receptor was blocked. In contrast, in this same species effects of oxytocin on social reward required access to the oxytocin receptor (Song, Borland, Larkin, O'Malley, & Albers, 2016).

Interactions between vasopressin and oxytocin help to explain the importance of social behavior in the regulation of anxiety and responses to threats, which in some cases are promoted by vasopressin (Neumann & Slattery, 2016). Thus, together oxytocin and vasopressin, and their receptors, create a biological and genetic pathway that regulates attachment and bonding (Carter, 1998, 2014). Both peptides also are capable of modulating the autonomic, immune, and metabolic systems acting to coordinate increases or decreases in the responses in these systems in the face of challenge.

Table 3. Animal Models for Studying the Biological Bases of Pair Bonding

Maternal–infant bonding:
Selective: Mothers show exclusive care for their offspring, e.g., sheep.
Maternal behavior:
Not selective, but may share physiological substrates with pair bonding, e.g., rats and voles.
Adult pair bonding:
Selective: Socially monogamous mammals showing a partner preference, e.g., prairie voles and titi monkey.

OXYTOCIN AND VASOPRESSIN SYSTEMS ARE AFFECTED BY EARLY LIFE EXPERIENCE

Oxytocin and vasopressin help to regulate social behavior across the lifespan. The plasticity of these systems provides mechanisms through which experience adapts to and prepares the body and behavior for future challenges. This assumption is supported by research evidence from humans (Feldman, 2017; Toepfer et al., 2017) and other animals (Carter, Boone, Pournajafi-Nazarloo, & Bales, 2009; Hammock, 2015) indicating that the effects of oxytocin are moderated by early life experiences. Research in prairie voles (Table 3) revealed that effects of oxytocin and vasopressin on later social bond formation could be detected as early as the first week of life, and are likely influenced by prenatal exposure to these peptides as well (Bales, Boone, Epperson, Hoffman, & Carter, 2011; Carter, Boone, Pournajafi-Nazarloo, & Bales, 2009). These effects occur, in part, because the expressions of receptors for oxytocin and vasopressin can be modulated by both genetic and epigenetic processes.

In humans it is likely that social attachments formed around the time of puberty reflect the interactions of vasopressin and oxytocin. Vasopressin is sexually dimorphic and increased in the brain by androgens, both during early development and in adulthood (De Vries & Forger, 2015). At optimal levels both oxytocin and vasopressin may contribute to the dampening of social anxiety, which would permit the approach to unfamiliar others. Following the establishment of a social bond, optimal levels of the same peptides may be involved in initiating the processes required to defend a partner against intruders or other suitors, including an experience that humans term “jealousy.”

THE ABSENCE OF OR DISRUPTIONS OF ATTACHMENTS

Nurture in early life is protective across the life cycle (Welch & Ludgwig, this issue). However, most of the evidence for the effects of early experience comes from maternal separation or other disruptions of the maternal–infant relationship (Bowlby, 1969). In primate infants the absence of adequate maternal care and opportunities to form attachments has been associated with growth retardation, social withdrawal, and atypical social behaviors (Harlow, 1971). In humans, data come primarily from epidemiology and correlational studies. In the face of maternal deprivation or broken social bonds—especially after extreme traumas including sexual abuse, episodes of recurring distress—physical disorders and vulnerability to illness are increasingly obvious (see Fox, Nelson, & Zeanah, this issue; Toepfer et al., 2017).

The consequences of disrupted attachment may emerge as psychopathologies, including personality disorders (MacDonald, Berlow, & Thomas, 2013), vulnerability to drug abuse, and addictions (Buisman-Pijlman et al., 2014; Chambers & Wallingford, this issue; Zou, Song, Zhang, & Zhang, 2016). There is increasing evidence for genetic and epigenetic differences that may contribute to the capacity of individuals to cope with early life adversity (Bradley, Wingo, Davis, Mercer, & Ressler, 2013; Feldman, Monakhov, Pratt, & Ebstein, 2016; Myers et al., 2014; Rijlaarsdam et al., 2017; Smearman et al., 2016; Toepfer et al., 2017). From this field of study is emerging strong evidence for the importance of oxytocin pathways, including oxytocin and vasopressin and their receptors, in the adaptive consequences and benefits of human attachment.

The behaviors and physiological changes associated with loss of an attachment figure, including bereavement or grief, are similar to those used to define depression. Animal research suggests that forced social separations or the absence of social attachments can trigger stress, anxiety, fear, and shut-down behaviors (Porges, 2011; Sun, Smith, Lei, Liu, & Wang, 2014). Some, but not all, of the effects of social isolation (Grippo, Trahanas, Zimmerman, Porges, & Carter, 2009; Grippo et al., 2012) or trauma (Frijlilng, 2017) can be prevented or reversed with exogenous oxytocin. Understanding the nature of physiological processes that regulate both the formation and dissolution of social attachment is essential in developing biologically informed treatments for disorders such as depression or trauma.

The effects of oxytocin and vasopressin on brain-body connections help to explain the profound health-related effects of relationships or their absence. Oxytocin and vasopressin interact to regulate the auto-

nomic nervous system, especially in the face of stress (Porges, 2011; Yee, Kenkel, & Frijling, 2016). Autonomic actions of oxytocin and vasopressin play a role in the capacity for and expression of social bonds that arise in the face of challenge or adversity. It is likely that the capacity of these peptides to integrate the activity of different branches of the autonomic nervous system helps to explain the importance of attachment in different forms of emotion and emotion regulation. These same peptides also have effects on the immune and metabolic systems across the lifespan, helping to explain the lasting effects of emotional experiences on physical health and well-being (Amini-Khoei et al., 2017; Hammock, 2015; Welch & Ludwig, this issue).

SOCIAL BEHAVIOR HAS A DIFFERENT BIOLOGY IN MALES AND FEMALES

In the mammalian brain vasopressin synthesis is sexually dimorphic (De Vries & Forger, 2015). There is emerging evidence that responses to exogenous vasopressin are different in males and females (Carter et al., 2009; Stribley & Carter, 1999; Thompson, George, Walton, Orr, & Benson, 2006). These responses may be supported by steroids including estrogen, progesterone, and androgens. However, steroid-peptide interactions in behavior are time-dependent, complex, and poorly understood.

Vasopressin, and associated increases in the sympathetic nervous system, would allow more active or mobilized responses to challenge, including the capacity for aggression and physical violence. At the same time, it is possible that a male-biased dependency on vasopressin might explain the tendency of males to form social bonds in the face of extreme challenges such as war. Dependence on vasopressin would leave males more vulnerable to disorders characterized by reductions in social behavior and leading to increases in aggression and risk taking (Carter, 1998, 2007; Taylor, Saphire-Bernstein, & Seeman, 2010). Concurrently, males may be protected, via vasopressin and associated increases in alertness or arousal, against shut-down responses including those that characterize some forms of depression, trauma, and PTSD.

Females also produce and rely on the physiological effects of vasopressin. However, social behaviors in females may be more dependent on estrogen and estrogen-oxytocin interactions. Females are more vulnerable to disorders associated with these same shut-down responses including depression and PTSD. Females in turn may be especially dependent on oxytocin. In the presence of deficiencies in either oxytocin

or its receptor, females may be more vulnerable to disorders characterized by passive responses.

Sex differences in the biology of attachment are in general adaptive, especially in the context of sex differences in the demands of reproduction. Both vulnerabilities and resilience are sexually dimorphic. Sex differences are generally most apparent in the face of stressful experiences, including social and hormonal experiences in early life (Carter et al., 2009). Moreover, sexual dimorphism in systems related to attachment and social behavior also help to explain sex differences in the vulnerability to disorders such as depression or autism (Carter, 2007), which often involve disturbances in social behavior. Knowledge of sex differences in the functions of oxytocin and vasopressin are needed in the development of treatments for a variety of mental and physical disorders including substance abuse, schizophrenia, and trauma (Carter, 2007; MacDonald, Berlow, & Thomas, 2013; Rubin et al., 2014).

EARLY LIFE EXPERIENCES INFLUENCE THE CAPACITY FOR SUBSEQUENT ATTACHMENT

Behavioral flexibility, possibly mediated in part by oxytocin and vasopressin interactions during development, allows individuals to adapt their social systems to accommodate early experiences and environmental demands. Animal research suggests that at least some of the effects of early experience are epigenetic, modifying DNA and creating the potential for transgenerational transmission of the tendency to form social bonds (Perkeybile & Bales, 2015).

Vasopressin expression may increase following neglect or other negative social experiences in early life (Hernandez et al., 2016; Murgatroyd et al., 2009). We hypothesize that early adversity could also upregulate the vasopressin receptor, especially in brain regions necessary to allow mobilized responses in later life and possibly affecting the capacity to form attachments.

Research in voles indicates that vasopressin can be developmentally regulated by oxytocin, contributing to the capacity to form pair bonds (Bales, Lewis-Reese, Pfeifer, Kramer, & Carter, 2007). In male voles a single oxytocin exposure in early life increased the expression of the vasopressin receptor in brain areas associated with pair bonding; while in both sexes exposure to exogenous oxytocin reduced the expression of the vasopressin (V1a) receptor in other brain areas (Bales, Plotsky, Young et al., 2007). In another experiment in prairie voles dose-dependent increases in vasopressin in the first week of life were followed by

increases in aggression in adulthood; these effects also were most apparent in males. The effects of early vasopressin on female aggression were weak and in females high doses appeared to inhibit later aggression (Stribley & Carter, 1999). The mechanisms underlying sex differences in the behavioral response to exogenous vasopressin remain to be understood. It is useful to recall that vasopressin is sensitive to stressors and also diet; for example salt releases oxytocin. In addition, nicotine is a potent regulator of vasopressin, so smoking, including prenatal exposure of the fetus, holds the potential to adjust this system with effects that likely differ between males and females.

Evidence from rodents also has revealed that levels of perinatal stress and varying amounts of parent–young stimulation contribute to the development of species-typical patterns of defensive aggression (Perkeybile & Bales, 2015). As one example from prairie voles, either reductions in early stimulation or excessive handling during the first week of life, both probably mediated by reduced parental care, were associated with a reduced capacity later in life to form social bonds (Carter et al., 2009). Differential early experience also was associated in adulthood with changes in central oxytocin and vasopressin and in the expression of vasopressin receptors (Bales, Boone, Epperson, Hoffman, & Carter, 2011; Bales, Lewis-Reese, Pfeifer, Kramer, & Carter, 2007).

In humans and other mammals, adaptive changes in the oxytocin and vasopressin systems, especially in early life, may alter brain receptors and their functions, possibly unregulating the oxytocin peptide or its receptor. These in turn could facilitate the capacity for attachment and also the development of adaptive resiliency across the lifespan. There is increasing evidence, including research in humans, that the response to exogenous oxytocin is moderated by early life experiences, including perceived attachment security or its absence. The release of endogenous oxytocin also has been related to early childhood abuse, with lower levels in individuals who have experienced greater emotional adversity in early life (Heim et al., 2009; Toepfer et al., 2017). Moreover, the release of oxytocin differs according to the adult attachment style of the individual. For example, a lower level of increase in oxytocin in response to a stressor was seen in individuals with a "dismissive" attachment style, compared to more securely attached individuals (Pierrehumbert, Torrisi, Ansermet, Borghini, & Halfon, 2012).

Early social history seems to be of particular importance to the capacity of oxytocin or the oxytocin receptor to buffer against various disorders. As one clinical example, neglect or abuse, especially in early life is associated with risk for the symptoms of borderline personality disorders (BPD), defined by hypervigilance toward perceived threats and atypical expressions of attachment. In some cases of BPD, oxytocin

treatments administered in adulthood may be helpful (Brune, 2016). However, in other cases, treatment of individuals with BPD with oxytocin was associated with increased symptomology, including distrust (Bartz et al., 2011). Animal models and human studies of responses to intranasal oxytocin suggest that the actions of exogenous oxytocin are dose-dependent and affected by early experiences. We specifically hypothesize that oxytocin may act through effects on vasopressin receptors. These effects are likely to differ according to the gender and social history of the individual. Thus, apparently "paradoxical" actions of oxytocin might be explained in part by the capacity of oxytocin to either stimulate or depress activity in the vasopressin system. In the face of a severe challenge, oxytocin could initially support an increase and activation of the sympathetic nervous system and other components of the HPA system. A large pulse of oxytocin also might acutely activate vasopressin receptors, further supporting mobilization and potentially defensive or aggressive responses.

In summary, the interactive effects of vasopressin and oxytocin during development are only gradually being recognized. The effects of oxytocin and vasopressin are different in males and females, especially in the face of stressful experiences or trauma in early life. Our research with prairie voles has revealed lasting effects of a single perinatal exposure to oxytocin (Carter et al., 2009) or a single handling experience on the first day of life. Positive parenting (versus neglect) has lasting behavioral consequences, possibly also through tuning of the oxytocin/vasopressin pathways (Perkeybile & Bales, 2015; Welch & Ludwig, this issue).

SOURCES OF INDIVIDUAL DIFFERENCES

Individual differences in the genetics/epigenetics of the oxytocin pathways are associated with differences in social behavior and in the response to stressors. Changes in exogenous peptides, especially in early life, are components of an adjustable system that helps the mammalian body predict and manage social behaviors and other challenges. The ability to form or express social bonds also can be disrupted by events that alter the oxytocin and vasopressin systems. Data from animal models and human epidemiology suggest that routine medical interventions (for example, oxytocin [Pitocin] use to induce labor, opioid medications that block the oxytocin system, or caesarean sections that alter exposure to endogenous oxytocin) have lasting consequences for the offspring and/or mother (Hayes, Balaban, Smith, Perry-Jenkins, & Powers, 2010; Kroll-Desrosiers et al., 2017; Song et al., 2017). Our ongo-

ing animal research suggests that such exposures could have epigenetic efects on the oxytocin systems, including changes in DNA methylation. Such changes in turn might produce reductions in the expression of receptors for oxytocin, leaving individuals less able to respond to oxytocin, and possibly more vulnerable to the defensive effects of vasopressin.

Based on this emerging literature, we specifically hypothesize that individual differences in responses to oxytocin could reflect individual differences in the sensitivity of the oxytocin and vasopressin receptors. A reduction or upregulation in the availability of the oxytocin or vasopressin receptors may be due to genetic variation and/or epigenetic tuning of this system (Bradley, Wingo, Davis, Mercer, & Ressler, 2013; Feldman, Monakhov, Pratt, & Ebstein, 2016; Myers et al., 2014; Rijlaarsdam et al., 2017; Rubin et al., 2014; Smearman et al., 2016; Toepfer et al., 2017). Particularly intriguing is the possibility that the capacity to release peptides or to respond to these could be affected by the attachment experience and trauma history of the individual.

Building on basic research, peptide-based interventions are being developed for the treatment of an array of human disorders (Feldman, 2017; Frijling, 2017; MacDonald, Berlow, & Thomas, 2013). Data from acute or short-term studies of therapeutic effects of oxytocin are encouraging. However, under some conditions, including chronic use or exceptionally high doses, exogenous oxytocin may downregulate its own receptor. Furthermore, in individuals sensitized by a trauma history, even acute oxytocin may activate defensive responses. Because of the broad and epigenetic actions throughout the body of the hormones that regulate attachment, experiences or manipulations that involve attachment and the hormones associated with these deserve careful study.

SUMMARY

Research in humans and other mammals indicate that oxytocin, vasopressin, and their receptors, are involved in the development of the capacity to form new attachments (Carter & Keverne, 2017). These systems provide neural substrates for positive social responses toward partners and in some cases selective aggression toward strangers. In general oxytocin and activation of the oxytocin receptor permit positive social behaviors and act as signals for psychological safety. In response to a challenge, increases in the activity of the oxytocin system allow passive coping, immobilization without fear, and positive social be-

haviors. However, interactions between oxytocin and vasopressin and their receptors are complex and not well understood.

The vasopressin system is more often associated with anxiety and mobilization in response to stressor or traumatic events, especially in males. Together these peptides serve to permit optimal parental and sexual responses. Individual differences in the expression of the oxytocin receptor, as well as differential sensitivity of the vasopressin receptor(s) may help to explain individual differences in the vulnerability to disorders, such as postpartum depression (Bell et al., 2015), characterized by anxiety and atypical social behaviors. These relationships, with consequences for both parents and children, need further empirical study.

The mechanisms remain poorly identified through which healthy social attachments increase resilience and the absence of social bonds increase vulnerability. The literature supports the notion that this system is sexual dimorphic, especially in its response to stress and adversity. Both oxytocin and vasopressin and their receptors, are regulated by steroid hormones and early experiences. Birth interventions, lactation, and patterns of parenting are capable of altering these systems, with effects that have been largely ignored and which should be studied (Harris & Carter, 2013).

We propose here that oxytocin/vasopressin pathways including peptides and receptors are essential to normal attachment. These also play an important role in all aspects of behavior that are directly or indirectly dependent on relationships and attachment. Behavioral experiences associated with attachment are likely to play a direct role in the capacity of individuals to respond to oxytocin and vasopressin. Based on their evolution and the broad consequences of oxytocin and vasopressin for behavior and physiology it is not surprising that early life experiences, as well as social bonds and attachments profoundly influence mental and physical health across the lifespan.

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