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Chapter 4

Peptide Pathways to Peace

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Abstract

Humans are capable of premediated aggression and warfare. In a war-torn world it is tempting to forget that we are highly affiliative primates, whose survival as a species may have been based on the capacity to live and reproduce in groups (Hrdy 2009). War and peace are dependent on human behaviors, which rely on interactive and overlapping physiological substrates. Despite experiences of aggression, abuse, or neglect, most humans have sufficient mental resources to exhibit positive social behaviors, social cognitions, and motivation for social attachment. Our physical survival and mental health requires "others." This apparent paradox, as well as the search for social safety arises, because the nervous system and behavior of contemporary humans are products of evolution. The purpose of this essay is to examine specific neuroendocrine pathways that may influence the positive social behaviors necessary for peace, when peace is defined as social safety within a society. This definition emphasizes the enabling power of social safety in promoting positive "states" associated with individuals interacting, socially connecting, and being mutually responsible for each other. Peptide pathways, including those reliant on oxytocin and vasopressin and their receptors, function as an integrated system mediating states of social safety. These endocrine and genetic pathways are at the center of a network that permitted the evolution of the human nervous system and allowed the expression of contemporary human sociality. Affiliation, pair bonds and other forms of prosocial behaviors are not simply the absence of aggression. Rather the prerequisites for peace, including prosocial behaviors and social safety, are built upon active peptide systems that are now becoming apparent and will be reviewed here. Knowledge of neurobiological mechanisms that form the foundations of social bonds and restorative behaviors offers a rational perspective for understanding, preventing or intervening in the aftermath of adversity, and enabling the emergence of peace in human societies.

Introduction

Since the end of the Second World War, 248 armed conflicts have been active in 153 locations worldwide (Themner and Wallenstein, 2012). The civil conflict in Syria provides a snapshot of the effects of an unsafe environment, which may be particularly disastrous for children. For example on August 23, 2013, the number of children registered as refugees

from Syria hit the one million mark. Child psychologist, Dante Ciccetti (2013:403–404) summarizes the lasting implications of maltreatment for early child development as follows:

> "Child maltreatment constitutes a severe, if not the most severe, environmental hazard to children's adaptive and healthy development… Specifically, maltreated children are likely to manifest atypicalities in neurobiological processes, physiological responsiveness, emotion recognition and emotion regulation, attachment relationships, self system development, representational processes, social information processing, peer relationships, school functioning, and romantic relationships… These difficulties pose significant risk for the development of substance abuse and psychopathology across the life course… Furthermore, there exists an increased risk for abused and neglected children to perpetuate maltreatment with their own offspring."

Nonetheless, contemporary humans are adaptive and reproductively successful in ways that few other large mammals can match. The interplay between social and aggressive traits of humans permitted the survival of *Homo sapiens* under historically difficult conditions. It has been proposed that our Neandertal cousins became extinct because they were less able than humans to create viable social groups (Pearce et al. 2013).

In 2011 the population of the world passed 7 billion and by 2024 is expected to exceed 8 billion. The development of agriculture and the industrial revolution have allowed the human population to explode. Humans are fundamentally social. However, war, rapidly expanding populations and other adversities can challenge the capacity of humans to be social and cooperative.

The Biological Origins of War and Peace

Behaviors that are described as threatening or aggressive can be cognitive and comparatively nonemotional, such as the decision to use chemical warfare or deliver bombs in unmanned missiles. Or, they may be highly emotional and defensive, sometimes leading to direct physical aggression and homicide. However, even emotionally-motived aggression does not necessarily lead to war (Fry and Soderberg 2013; Fry this volume). The feelings and states that lie at the heart of defensive or reactive aggression probably have somewhat different biological and genetic substrates than planned "strategic" forms of aggression. Although the neurobiology of human aggression is beyond the scope of this paper, defensive behaviors are central components of human sociality. Thus, it is difficult to separate the biological substrates of peace from those of war and aggression. Multidisciplinary perspectives from evolution, phylogeny, neuroendocrinology, genetics, and development of the mammalian nervous system are critical to understanding both positive and negative patterns of behavior. Studies linking positive behaviors to the anatomy and physiology of the nervous system have increased dramatically, especially over the last two decades. A new and more positive perspective on human behavior is emerging from these studies. This perspective is built upon the hypothesis that prosocial behaviors, including social bonds and loving relationships, have distinct biological substrates (Carter 1998; Porges 1998; Carter and Porges 2013).

Peace as a psychological concept has generally been considered in the context of human behavior and is often described as the absence of negative experiences. However, as with aggression and other negative experiences, the positive behaviors and psychological states that are associated with peace also are based on ancient biological systems. We will argue here that hormonal and neural processes allow the emergence of states, experienced as peaceful, which are shared among social mammals. Consistent with other chapters in this volume, we will focus on the individual, defining peace as a positive state of mind derivative of social safety and emotional experiences associated with feeling calm and tranquil. The emotional states and experiences of the individual translate into relationships, and have consequences for families, communities, nations and ultimately affect the future of our globe. To provide context a few foundational assumptions that guide this perspective are offered below.

Working Hypotheses and Assumptions

Evolution and Development

In response to conditions of extreme adversity and maltreatment, individual variation is common and some individuals are resistant to the lasting effects of trauma even in early life (Ellis et al. 2011; Cicchetti 2013). Adaptation and resilience in the face of adversity have biological causes and consequences, including effects on growth and development. In addition, adaptation and resilience are often described in terms of differential activity in the hypothalamic-pituitary-adrenal (HPA) axis, as well as differential responsivity to adversity (sometimes termed diathesis-stress) (Hostinar et al. 2013). Research from a variety of sources suggests that some individuals seem to primarily respond to and are shaped by positive experiences, rather than by adversity. The sources of these individual differences are not well identified, but are at least in part biological, with genetic/epigenetic underpinnings.

Understanding the evolutionary and developmental origins of the mammalian nervous system provides critical insights into the variations in social and emotional behaviors that characterize contemporary humans. Across evolutionary time, these systems responded to the adaptive demands of individual survival and reproduction (genetic survival). In the current human population, broad variation exists in behavioral phenotypes, including the responses to positive or negative environmental conditions. These are presumed to reflect individual differences in “differential susceptibility,” based at least in part on individual differences in the “neurobiological sensitivity to context” (Ellis et al. 2011). Such variations may be adaptive depending on environmental context and demands. As described below, mechanisms for these differences may be found in an understanding of two ancient peptides – oxytocin and vasopressin. We propose that knowledge of these processes could lead to a new science of child development - a perspective that is shared by others (reviewed by Feldman 2012; Hostinar et al. 2013).

Genetics, Epigenetics, and Behavior

Human behavior is, in part, a product of inherited genetic codes, which in turn guide the assembly of biochemical molecules into tissues including the nervous system. At least some processes, presumably adaptive at some point in our evolutionary past, are retained in our anatomy and physiology. Among the products of our genes are hormones, neurotransmitters, neuromodulators and receptors which regulate the functions of those tissues.

The mammalian nervous system and genome can be physically and functionally altered by behavioral experiences, especially in early life. However, studies directly connecting *specific* behavioral experiences to *specific* neuroanatomical or neuroendocrine changes remain scarce. Much of what we know about development and behavior is based on correlations that do not prove "causation."

Short- and Long-Term Perspectives on Neuroplasticity and Adaptation

The human body, and especially the nervous system, adapt in response to a changing and challenging environment. Included in the genome are genetic programs that influence the capacity of the nervous system to modify itself. Rather than being "hard-wired," mammals, and especially humans have inherited a nervous system with "plastic" components that appear designed to be changed, both through "learning" and comparatively long-lasting, epigenetic processes which allow us to incorporate new information into the genome.

Both positive and negative social behaviors rely on neural substrates that were inherited, in part, from our premammalian ancestors. In the face of extreme stressors, older systems, based on our phylogenetic past, may take precedence. For example, the "shut-down" adaptations that emerge in the face of trauma rely on ancient neural systems that are not easily addressed by our modern cognition (Porges 1998; 2011). Evolutionarily older components of the nervous system, especially in the brainstem, may be less capable of adaptation than more modern neocortical systems. However, even ancient systems can be profoundly affected by both positive and negative experiences.

The developing nervous system is physically and biochemically sculpted by social interactions. Experiences, especially in early life, can epigenetically regulate gene expression (Champagne 2012; Zhang et al. 2013; Kumstra et al. 2013). Social experiences during sensitive periods, including prenatal, perinatal and adolescent development, may be of special significance to social and emotional behavioral traits in later life. In addition, acute versus chronic responses to challenge differ physiologically. Reactions to stressful or negative experiences may in the short term appear advantageous. However, chronically negative and stressful experiences are costly in a longer time scale, creating vulnerability to emotional and physical diseases (Cicchetti 2013; Tol et al. 2013).

Research in monkeys or humans reared without a mother or consistent caretaker (Fox et al., this volume) confirms the hypothesis that appropriate parenting is important for primate social and emotional development. Social interactions are beneficial throughout life, and the absence of social support or a perceived sense of loneliness increases vulnerability to many forms of mental and physical disorders.

Stressful early experiences can produce a variety of changes, such as a smaller body size or atypical sociality in later life. Such changes might be deleterious in some environments, but adaptive in others, depending on individual differences, experience, resources and context (Ellis et al. 2011). Understanding evolutionary and contemporary context is critical to evaluating the impact and mechanisms for a given experience (Bartz et al. 2011).

Neuroendocrine Perspectives on Mammalian Social Behavior

The Social Nervous System

Positive social behaviors are not simply the absence of aggression or other forms of pathology (Carter 1998). Rather, neural structures and mechanisms form the basis for active behavioral responses that lead to affiliation, selective social attachment, empathy and other prosocial behaviors. These behaviors include the willingness to approach and trust others, and to use other people to manage emotions, such as fear or trauma in the presence of maltreatment or stressful experiences (Feldman et al. 2014).

Embedded in the human brain is a circuitry that has been described as the “social nervous system” (Adolphs 2009). Mammals also have an evolved “social engagement system,” with the biological and behavioral capacity for both positive social behaviors and physical and behavioral reactions to threat (Porges 2011). The social engagement system includes nerves that calm our hearts and regulate facial expression, ingestion, vocalizations, and listening. This system, which is essential for social expression and communication, has the capacity to inhibit autonomic states that promote fight or flight behaviors. The social engagement system is an integrated system with common brainstem areas regulating visceral state (through vagal pathways), and the striated muscles of the face and head (through special visceral efferent pathways embedded in several cranial nerves). The innervation of this system relies on at least some of the same hormonal processes that are also implicated in the central and autonomic regulation of social behavior. The accessibility of this system is dependent on cues in the environment that trigger a sense of safety to promote social connectedness, or trigger a sense of danger to promote flight/ flight behaviors, or trigger life threat responses associated with fainting, defecating, and dissociation.

The Autonomic Nervous System and Physiological Adaptations Linking Sociality and Health

The same neural systems that regulate emotional behaviors and social communication also regulate the physical body. Understanding basic physiological processes allows us to reconceptualize social behavior and the social nervous system as core features of the body’s integrated system of health and restoration. Of special importance to both survival and social and emotional behaviors is the autonomic nervous system (Porges 2011). Older brainstem and autonomic systems, including the vagus, are necessary for vegetative and growth processes. These autonomic systems supply oxygen and energy to the brain via

cardiovascular, respiratory and metabolic pathways, and also regulate the immune and reproductive systems.

The mammalian nervous system is constructed upon a hierarchical template with evolutionarily older systems having impact on more recently evolved systems. The demands of ancient vegetative systems, including those that support life and reproduction, may override those of the more cognitive or rational neocortex. These phylogenetically ancient systems also serve the survival and reproduction of the species and help to account for behavioral states and traits.

In a safe environment the healthy human nervous system generally exhibits positive social behavior. In an unsafe or threatening environment, defensive or aggressive behaviors are more likely to appear. Mammalian sociality is based on evolved anatomical and neurochemical substrates that serve social communication and cognition. These systems are regulated by both the central and autonomic nervous system, integrating voluntary and involuntary expressions of social cues and emotions (Porges 2011). Humans are especially responsive to facial cues and acoustic signals. Because these can express social safety or threat, they may be particularly powerful channels of communication.

Mammalian Reproduction and Motherhood Shape the Nervous System.

Placental mammals provide nurturance for their offspring throughout gestation and during lactation. In some species prolonged maternal care exists, including defense of the offspring during the postpartum period. The unique physiological adaptations of placental mammals are associated with high levels of social behavior and may support the development of a comparatively larger neocortex. The placenta is regulated by the paternal and maternal genome, allowing the parents to further influence the growth and size of their offspring (Keverne, this volume).

The intense maternal investment that is provided by mammals, and especially by human mothers has the consequence of supporting the development of the young during periods of vulnerability. In humans lactational hormones can be contraceptive, allowing birth spacing, thus increasing the access of offspring to their biological mother and her resources. Even among primates, humans have an exceptionally long period of maturation. Developmental processes, including growth of the neocortex, can continue past reproductive maturity (Carter 2014). Under optimal conditions this allows a protected period during which the neocortex can develop. During this period various forms of learning, including social cognition and the formation of social networks may be facilitated (Hrdy 2009). Social synchrony between caretakers and children also can be emotional learning experiences for the offspring, enhancing both prosocial behavior and the capacity for emotion regulation in later life (Feldman 2012). Furthermore, family or group living facilitates successful reproduction and fitness.

Maternal Behavior as a Prototype for Social Behavior.

It can be argued that maternal behavior is a biological and behavioral prototype for other forms of sociality (Carter 1998). At the endocrine center of social behavior are oxytocin and

vasopressin. The same hormones that facilitate birth and lactation, also promote maternal behavior and maternal defense of the young. Small mammals, such as mice are capable of birth and maternal behavior even in the absence of oxytocin. However, milk ejection and nursing are not possible in mice mutant for the gene for oxytocin or its receptor, suggesting that lactation is a fairly recently evolved trait and is oxytocin-dependent.

Lactation is unique in mammals and may depend on physiological functions of oxytocin that arose during the evolution of mammals (Carter 1998). In addition, milk contains a variety of hormones, including oxytocin and probably vasopressin, which may be involved in tuning the nervous system of the offspring to adapt to environmental changes. For example, in milk high levels of oxytocin might be associated with periods of resource abundance, while high levels of vasopressin might reflect periods of stress or limitations of resources such as water or food. Lactation - especially frequent and nocturnal nursing - has the capacity to regulate maternal physiology and suppress the return to ovarian cyclicity after birth. 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.

Hormones in human milk may serve as a form of social and endocrine communication between mother and baby. The lactating mother also has reduced reactivity to stressors (Carter 1998). These adaptations increase the behavioral flexibility of the parent in the face of the demands of child rearing and can modify the behavior and physiology of the infant, with consequences that vary according to environmental demands and with the history of the mother.

The neurobiological substrates for a long gestation, forceful birth, and postnatal nutrition in the form of lactation allowed the emergence in mammals of an increased brain size. 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, this volume). Delivering a large baby, which involves prenatal maternal investment, cervical stimulation, and the release of oxytocin, as well as stress and pain in birth, also may increase the attachment between the mother and child. Furthermore, it is likely that these same processes were critical in permitting the evolution of modern human social cognition and language (Carter 2014).

Oxytocin and Vasopressin Pathways

Properties of Oxytocin

Oxytocin is a nine amino acid peptide hormone composed of a six amino acid ring and a three amino acid tail. At least some of the functions of oxytocin and vasopressin may be explained by the dynamic biological properties of the sulfur bonds that create the ring in oxytocin. These bonds allow the oxytocin molecule to form temporary and long-lasting

unions with other chemical entities, with dynamic functions that remain to be described (Martin and Carter 2013).

Receptors for oxytocin are localized in areas of the nervous system that regulate social and adaptive behaviors, including the hypothalamic pituitary adrenal (HPA) axis, and the autonomic nervous system. Only one oxytocin receptor (OXTR) has been described, which is present in neural tissue and in other parts of the body including the uterus.

Variations in the gene for the oxytocin receptor (*OXTR*) have been associated with variation in social behaviors, including the atypical behaviors that characterize autism spectrum disorders (ASD) (Jacob et al. 2007), but also in healthy individuals (van IJzendoorn and Bakersman-Kranenburg, this volume). In addition, hypermethylation of the OXTR, which may silence that gene, also has been detected in ASD (Gregory et al. 2009). The capacity of the OXTR to be genetically and epigenetically regulated (possibly by early life experiences), brings up important questions about the origins of individual differences in social behavior and in the sensitivity to social context and adversity. For example certain single nucleotide polymorphisms (SNPs) in the *OXTR* have been associated with heightened sensitivity to social cues or their absence (Riems et al. 2014; Hostinar et al. 2014; Dabbs et al. 2014; Feldman et al. 2014) and more empathetic emotional and physical responses to the pain of others (Smith et al. 2014).

Oxytocin is found in high concentrations in the paraventricular (PVN) and the supraoptic nuclei (SON) of the hypothalamus. Following synthesis in the PVN and SON, oxytocin is transported to the posterior pituitary, where it is released into the blood stream. Oxytocin also is released within the brain, reaching targets throughout the nervous system with direct behavioral consequences (Neumann and Landgraf 2012). Outside of reproduction, the exact nature of the stimuli that release oxytocin is poorly understood. However, it is known that oxytocin can be released in response to a variety of social experiences and under circumstances that are both positive and negative (Ebstein et al. 2012; Feldman 2012; Neumann and Landgraf 2012).

Oxytocin normally is produced tonically and individual blood levels tend to be consistent across time (Dai et al. 2012; Feldman 2012). Oxytocin release also can be pulsatile; unique plasticity in oxytocin synthesizing cells allows physical transformation in response to social and hormonal stimulation. Stimulation of the oxytocin system also can “feed forward” to release more oxytocin. Oxytocin can be released in a coordinated fashion, within the brain and at the posterior pituitary, into the general circulation (Neumann and Landgraf 2012). It is likely that the ability of oxytocin to have broad and synchronized behavioral and physiological consequences, increasing connectivity among brain areas, is related to this capacity for movement throughout the brain and body.

Oxytocin is exceptionally abundant 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), presumably translating into very high concentrations of the oxytocin peptide in the brain and blood. Measurement of oxytocin by mass spectromety indicates that this peptide is sequestered on plasma proteins, possibly available for local release as needed (Martin

and Carter 2013). Levels of oxytocin in blood and brain vary across species and individual differences in oxytocin are common. These have been related to individual traits, including social behavior and some of the novel patterns of behaviors associated with ASD, schizophrenia or unique behavioral phenotypes, such as the hypersociality seen in Williams syndrome (Dai et al. 2012).

Functions of Oxytocin

Oxytocin plays a major role in positive social behaviors and sensitivity to social cues. In general oxytocin has been associated with social interactions that involve positive sociality and contact, such as female sexual (Carter 1998; Porges 2011) and maternal behaviors (Feldman 2012). Oxytocin receptors are abundant in pathways that serve ancient visceral components of mammalian reproduction. However, oxytocin also may directly or indirectly influence more modern neural systems necessary for social engagement, allowing the high levels of social sensitivity and attunement necessary for human sociality and for rearing a human child. The behavioral patterns associated with oxytocin specifically include "immobility without fear," which is critical to several forms of positive social and reproductive behaviors in mammals (Porges 1998). Concurrently, oxytocin may reduce anxiety, reactivity to social stressors and aggression. Under optimal conditions oxytocin may reduce fear, serving as a biochemical metaphor for safety (Carter 2014).

Ties that Bind

Selective social behaviors and social bonds or attachments are components of emotionally loving relationships and healthy families in human societies. Social bonds often develop between family members or sexual partners. Whether human social bonds can be formed in the absence of oxytocin is not known. However, animal research, originally conducted in sheep (Keverne, this volume) and in the socially monogamous prairie vole (Carter 1998) suggests that oxytocin is necessary, but perhaps not sufficient for social bond formation.

Oxytocin can in general encourage emotional states which allow the use of others as emotional support during periods of stress and restoration (Hostinar et al. 2013; 2014; Feldman et al. 2014). Oxytocin may help to protect both mother and infant from the memory of pain associated with childbirth, thus further promoting attachment. Maternal oxytocin may protect her from postpartum depression (Stuebe et al. 2013), which has serious negative consequences for child development and family relationships.

Oxytocin Facilitates Growth and Healing

Oxytocin has therapeutic consequences that are only now being discovered including protective and healing effects on injured tissue. Among the restorative processes that oxytocin can affect are neurogenesis, cellular growth, differentiation, death or motility, and inflammation. The most complete work in this area has been done in the heart (Gutkowska and Jankowski 2012). In rodents, apoptosis (programmed cell death) in heart tissue can be inhibited by oxytocin and especially by the precursor or "fetal" form of oxytocin. Oxytocin holds the potential to literally heal a broken heart.

The effects of oxytocin may help to explain the well-documented association between social support and prevention or recovery from many disorders of brain and body including trauma (Carter 1998; Olff et al. 2013). Among the mechanisms for both social support and the beneficial effects of oxytocin are actions of this peptide on the autonomic nervous system, which in turn has consequences for sensory, visceral, metabolic and smooth motor systems. In addition, through actions on the autonomic nervous system, oxytocin may play a role in the maintenance of the blood supply to the cortex, allowing consciousness (Porges 2011).

Oxytocin is synthesized in the hypothalamus in an area known as the PVN. Because the PVN is a major site of convergence and integration for the HPA axis and autonomic function, oxytocin is positioned for a role in stress and emotion. Oxytocin also is co-localized with corticotropin-releasing factor (CRF), which regulates the HPA axis. CRF has been implicated in some of the detrimental effects of chronic stress. Thus, the co-release of oxytocin and CRF may be adaptive, allowing both mobilization in the presence of a challenge, followed by coping responses, including possibly increases in social motivation.

Across the lifespan oxytocin probably increases social sensitivity and modulates reactivity to stressors. Oxytocin dynamically moderates the autonomic and immune systems, with anti-oxidant and anti-inflammatory effects. These actions of oxytocin may help to explain the adaptive consequences of social behavior for emotional and physical health. Both directly and indirectly, oxytocin might facilitate the use of both prosocial and rational, versus emotional or aggressive, strategies in the face of challenge.

Properties of Vasopressin

Vasopressin also is a nine amino acid peptide with a six amino acid ring and a three amino acid tail. Vasopressin is structurally similar to oxytocin, with only two amino acids distinguishing the two molecules. Both arose from a common ancestral molecule. Like oxytocin, vasopressin is synthesized in the PVN and SON, although oxytocin and vasopressin usually are not present in the same cells. Vasopressin is found in several other brain regions including the medial amygdala (mAMY), bed nucleus of the stria terminalis (BNST) and lateral septum (LS). In this axis the effects of vasopressin are androgen dependent and thus usually male-biased (Carter 2007). In addition, vasopressin is found in the suprachiasmatic nucleus (SCN).

Three receptor subtypes have been identified for vasopressin. Of these, the V1a receptor, which is found in the brain, has been associated with social behavior, engagement and pair bond formation, especially in males. Both individual and species differences in V1a receptor distributions have been identified. Among the sources of these differences are species-typical variations in the promoter region of the gene for the V1a receptor (Hammock and Young 2005).

Functions of Vasopressin

Vasopressin is associated with active forms of coping and defense at several levels. The primitive functions of vasopressin were probably water retention, and other forms of adaptive defense of cells from environmental challenges such as dehydration. In mammals

this behavioral motif may have eventually been co-opted at the level of the organism to include defensive behaviors and some forms of aggression (Ferris 2008; Neumann and Landgraf 2012). As the functions of vasopressin evolved in more complex organisms they included defense of self, mate, offspring and resources. Vasopressin may be especially critical for forms of sociality that require mobilization and defensive arousal (Carter 1998). Vasopressin in the SCN plays a central role in biological rhythms, helping to coordinate activity, with rest and restoration.

Vasopressin (and oxytocin) may permit social approach in the presence of a novel conspecific, possibly by increasing social "bravery." Vasopressin also is important to autonomically mobilized forms of male parental behavior (Kenkel et al. 2012, 2013). Oxytocin and vasopressin systems seem to function in concert to allow selective social behaviors and male parental behavior, which involve social approach, nurturance and in some cases autonomic arousal, potentially in defense of a sexual partner or offspring or when new relationships are initially forming (Carter 1998; Porges 1998).

Vasopressin also may synergize with CRF to activate the HPA axis, potentially permitting stress reactivity, anxiety, and territoriality. Increased central vasopressin, and reductions in oxytocin have been associated with defensive aggression and, in human males, with emotional dyregulation (Lee et al. 2009). Vasopressin, CRF and other central hormones might help to create emotional states that reduce the capacity to use cognitive or "top down" strategies to manage stressful experiences. Overactivity in the vasopressin system would in theory lower the threshold to impulsive forms of aggression, although studies administering either oxytocin or vasopressin suggest that males and females respond differently to these peptides. Vasopressin elevates blood pressure and cardiovascular activity and may be implicated in the arousal associated with posttraumatic stress disorder (PTSD).

Interactions between Oxytocin and Vasopressin

Vasopressin and oxytocin have the capacity to bind to each other's receptors, and under normal conditions they are probably dynamically interacting. Under conditions of stress, both peptides may be released together or in tight synchrony. These interactions may facilitate rapid changes in behavioral and emotional states (Neumann and Landgraf 2012). Under some conditions (and especially with regard to behavior, emotional arousal, mobilization and autonomic functions) the behavioral effects of oxytocin and vasopressin can be opposing (Carter 1998). However, in other circumstances the effects of both peptides seem to be functionally similar (Kenkel et al. 2013). For example, exogenous oxytocin and vasopressin can both facilitate initial social approach and pair bonding in prairie voles. Whether the endogenous peptides have similar effects is less clear, especially since central vasopressin is androgen-dependent and associated with defensive behaviors in males, but less so in females (Carter 2007).

In adult males, including humans (Feldman 2012) and prairie voles (Kenkel et al. 2012), oxytocin and vasopressin may be released by infants and can facilitate parental behavior. The release of oxytocin in males by stimuli from the infant could facilitate coping in response to the complex needs of the infant. However, when reproductively naive males are exposed

to an infant they transition to a physiological state characterized by activation of both the sympathetic and parasympathetic branches of the autonomic nervous system. This somewhat novel physiological state, which probably depends on interactions between oxytocin and vasopressin, allows the simultaneous appearance of nurturing and active protective forms of social behavior (Kenkel et al. 2013).

The Effects of Oxytocin Are Not Always Prosocial

The arousal-enhancing effects of oxytocin, and presumably the release of oxytocin, differ widely among individuals and are likely influenced by genetics, context and social history. In the absence of a supportive rearing experience or the presence of a history of adversity, the effects of exogenous oxytocin may no longer appear prosocial or positive (Bartz et al. 2011). For example, neutral stimuli may be perceived as threatening. In the presence of a challenge the release of endogenous oxytocin might initially support arousal, including activation of the sympathetic nervous system and other components of the HPA system. For example, there are indications that perceived loneliness or isolation in early life also could alter the physiological consequences of exogenous oxytocin (Norman et al. 2011). Early maltreatment also has been associated with an increase in endogenous oxytocin (Seltzer et al. 2013). However, some individuals are much more sensitive than others to the consequences of maltreatment (Hostinar et al. 2014) or trauma (Feldman et al. 2014), and presumably to oxytocin as well (van IJzendoorn and Bakersman-Kranenburg, this volume).

Another example of the apparently paradoxical effects of high levels of oxytocin is seen in Williams syndrome, a genetic condition characterized by hypersociality but also anxiety; in this syndome high levels of oxytocin are associated with maladaptive social behaviors (Dai et al. 2012). Whether this atypical behavioral phenotype can be directly attributed to oxytocin, vasopressin, or interactions between these and other neurochemicals remains to be determined.

Without knowledge of the status or sensitivity of the oxytocin or vasopressin receptor, or other physiological variables we can only speculate about the possible mechanisms of effects of high levels of endogenous or exogenous oxytocin. For example, oxytocin appears to facilitate fear conditioning in humans (Acheson et al. 2014) and local effects of oxytocin in the septum of mice facilitate fear conditioning (Guzman et al. 2013). Large amounts of oxytocin also may activate vasopressin receptors, further supporting mobilization and potentially defensive responses. This might help to explain the tendency toward parochial behavior and “outgroup” rejection described in some studies after intranasal oxytocin (De Dreu 2012).

As with early life experiences in general (Ellis et al. 2011), the response to peptides, of either exogenous or endogenous origins, are likely to be context dependent and individualistic (Bartz et al. 2011; Feldman et al. 2014). Context, in turn, may influence other physiological process such as those regulated by sex steroids, opioids, catecholamines, and inflammatory cytokines. Patterns of autonomic response also would be expected to differ among individuals and by context (Porges 2011). Emotional contex is influenced by

autonomic sensations (Norman et al. 2011), and autonomic systems are targets for the actions of oxytocin (Carter et al. 2009; Carter and Porges 2013; Kenkel et al. 2013).

Developmental Consequences of Oxytocin and Vasopressin

Of particular importance to child development are effects of oxytocin and vasopressin during early development. Oxytocin present during the perinatal period can tune the central nervous system, potentially supporting adaptive patterns of physiology and behavior in later life. Oxytocin helps to protect the brain and heart from hypoxia, especially during birth. Circulating oxytocin acts as a signaling mechanism between the mother and fetus, and may help to protect and mature cortical cells during development (Khazipov et al. 2009; Tyzio et al. 2006; 2014; Kenkel et al., 2014). Through lactation and prolonged periods of postnatal nurture, oxytocin shapes the physical development of the brain, with a role in the genetic regulation of the growth of the neocortex, which is permissive for human cognition (Carter 2014).

In a series of experiments in prairie voles we examined the effects of manipulations of oxytocin in the first days of life (Carter et al. 2009). In general, exposures to low doses of oxytocin were associated with later increases in social behavior, while higher doses of oxytocin or treatments that blocked oxytocin were likely to interfere with normal patterns of social behavior including the capacity for pair bonding. Alterations in social behavior also were seen when mothers and infants were exposed to differential amounts of handling. Either repeated manipulations or reductions in stimulation could interfere with the later appearance of typical social behavior. In general, male voles appeared to be more sensitive than females to the long-term consequences of early experiences, possibly through alterations in the vasopressin systems. Alternatively, females may be resistant to some of the detrimental effects of early experiences, possibly due to protective epigenetic consequences of oxytocin (Carter et al. 2009).

Prairie voles of both sexes that were exposed to exogenous vasopressin the first week of life showed increased aggression in adulthood. This effect was stronger in males than females (Stribley and Carter 1999).

Synthetic forms of vasopressin, which reduce urine-production, are sometimes used to treat bed-wetting in children, with unexamined behavioral effects. Mechanisms for the developmental effects of peptides need further exploration, especially in light of the widespread clinical applications of synthetic oxytocin to induce or augment labor (Kenkel et al. 2014).

Sex Differences and Psychiatric Implications of Oxytocin and Vasopressin

Sex differences in the vasopressin system may have particular consequences for behaviors that are sexually dimophic, including male-biased disorders such as ASD (Carter 2007). Early onset schizophrenia also is more likely in males. In women diagnosed with schizophrenia (and receiving medication) there was an association between higher levels of oxytocin and fewer psychotic symptoms. In a separate study in unmedicated women

experiencing a psychotic episode vasopressin levels were elevated (Rubin et al. 2013). The effects of medications and gender on both oxytocin and vasopressin deserve further study.

Post Traumatic Stress Disorder (PTSD). Of special relevance to understanding the consequences of early life trauma, adversity and war-related experiences across the lifecycle is the clinical syndrome known as PTSD. Understanding the behavioral and emotional consequences of trauma requires awareness of the evolution of the mammalian nervous system (Porges 2011). Withdrawal of the myelinated vagus may leave an individual vulnerable to sympathetic overarousal and mobilization The responses that taken together comprise PTSD may reflect activity in older parts of the nervous system including unmyelinated vagal pathways, which involves a passive "shut down" strategy and immobilization. While adaptive in some contexts, the reactions that are follow traumatic or highly stressful experience can be disruptive to social engagement and other prosocial behavior, when manifest as either overactivation or "immobilization with fear" (Porges 1998). Thus, individuals who experience PTSD, may exhibit limitations in their abilities to subsequently regulate their emotional state in response to environment challenges.

PTSD can occur in both sexes. However, the phenotype of PTSD may be sexually dimorphic. Males may show a more aroused or mobilized form of response to trauma, while women can be differentially vulnerable to immobilizing or "shutting down" in response to trauma. Preliminary studies suggest that blood levels of endogenous oxytocin may be altered in PTSD, with profound individual differences that may manifest as individual differences in the peptide or receptor (Seng et al., 2013; Olff et al. 2013). The mechanisms for individual vulerability in disorders such as PTSD often include an early history of adversity, and might be associated with differential sensitivity in the oxytocin receptor (Feldman, et al. 2014). It is also possible that the absence of adequate maternal stimulation in early life can produce overactivity in the synthesis of vasopressin (Zhang et al. 2012) or altered sensitivity in the vasopressin receptor.

Although in early stages, research on the functions of oxytocin and vasopressin in emotional responses and coping holds promise for understanding individual and sex differences in a more general sense. It unlikely that males and females use oxytocin pathways in identical ways (Carter 2007), and one of these mechanisms for individual variations may be based on sex differences in the epigenetic consequences of early experiences.

Methodological Limitations

Interactions between oxytocin and vasopressin are an essential component of the capacity of these peptides to support dynamic behavioral change (Carter 1998; Neumann and Landgraf 2012). However, at present studies attempting to address real-time interactions between biochemical changes and social behavior have to be taken in the context of methodological limitations. For example, among the most directly translational approaches to studying human behavior are psychophysiological methods, such as continuous recordings of autonomic functions that appear to be comparable across species (Porges 2011; Carter et al. 2009). However, interpreting physiology in terms of complex behavioral experiences and emotions offers additional challenges.

Variable adaptive strategies allow some individuals to most fully flourish in good times, while others may survive and even prosper under adversity (Ellis et al. 2011). It is possible that the physiological basis of these response patterns will be shown to be based, at least in part, on sensitivity to, or responsivity to oxytocin- and vasopressin-based systems. Research testing this hypothesis in humans is now emerging. At present these are based primarily on individual variations in genes that regulate responses to oxytocin (Hostinar et al. 2014; Feldman et al. 2014). However, a more in depth understanding of the role of peptides in human behavior will require knowledge of not only receptor genetics, but also epigenetic modifications and the dynamics of the release and actions of the oxytocin and vasopressin peptides.

Animal research was the original source of most of our understanding of the peptide pathways described here. Historically, attempts to describe the role of peptides in behavior have been based on pharmacological manipulations using drugs that stimulate or block specific receptors' genetic manipulations. For example, in knock-out mice a gene for a hormone or receptor is permanently or temporarily inactivated. In a few cases endocrine measurements are made by dialysis of tissue-specific hormonal changes. However, because a comparatively large sample volume is needed to assay these hormones, the sampling rate is rarely frequent enough to match the pace of behavioral changes (Neumann and Landgraf 2012). In some cases elegant, tissue-based methods (usually done in rats) have been used to describe tissue-specific endocrine changes (Stoop 2012). Although all of these methods have limitations, taken together they support the assumption that the functions of oxytocin and vasopressin are both intertwined and in general rapidly changing, possibly approximating the time course of behavioral events, such as approach or avoidance.

The therapeutic importance of oxytocin is supported by reports of treatments for mental disorders including autism, schizophrenia, PTSD and addiction. Those findings are not described here, but are detailed in other reviews (for example, Ebstein et al. 2012; MacDonald and Feifel 2013; Acheson et al. 2013; Buisman-Pijlman et al. 2013).

Of course pharmacological approaches have many limitations and are not ideal for producing social change. The important goal for future research is to understand the naturally occurring mechanisms that regulate biological mechanisms, and to use this knowledge to create a science of peace and safety.

Questions and Challenges for Future Research

As we seek the biological foundations of peace or war, we face a variety of challenges. Understanding the contrasting physiology and health consequences between experiences of social safety and aggression is a major task for the behavioral and neural sciences of the 21st century. Many questions are still mired in our incomplete understanding of the fundamentals of mammalian biology. Others are based on methodological and theoretical limitations. Of particular importance to the concept of "peace" is the capacity to extract physiological patterns and predictors relevant to human social and emotional experiences, especially within groups. A few examples of these are described here.

Methodological challenges. Many practical and ethical considerations restrict the methodologies that are available for the analysis of behavioral physiology. The most common unit of analysis for behavioral research is the individual. However, social behavior inherently involves one or more others - or a mental representation of another. Social behavior also is dynamic and ideally reciprocal, thus creating daunting levels of complexity. Against this background, measurements of endocrine processes typically depend on samples taken at single or infrequent time points. The act of collecting endocrine samples can disrupt both physiology and behavior. Noninvasive and more frequent methods for collecting data will be critical to understanding the biological basis of social behaviors. The time courses possible for collecting endocrine or other physiological measurements may not necessarily correspond to the time course of behavioral changes in question. Physiological events may precede behavior by time periods which are variable. What is the developmental time course of endocrine process including peptides and their receptors relevant to a sense of peace? How do the developmental changes in peptides interact with the changing and usually expanding access to others? Are endocrine processes relatively stable across time, equating to "traits", or perhaps more variable in the face of environmental demands, possibly more equivalent to "states"?

Measurement of peptides has proven challenging. Questions have been raised regarding the reliability and validity of current assays for peptide hormones, including oxytocin and vasopressin. The most common assays rely on polyclonal antibodies and preparation of samples which can be variable across methods. Within the limitations of these methods, competently conducted radio-immunoassays or enzyme-immunoassays typically provide replicable data within and across subjects, and in some cases across studies. Dozens of studies using these methods support the hypothesis that measurements of peptides in bodily fluid can be related to behavioral outcomes (Ebstein et al. 2012; Weisman and Feldman 2013; Weisman et al. 2013). For example, we have recently compared plasma levels of oxytocin and vasopressin as measured by enzyme-immunoassays in individuals suffering from psychosis and their first-degree relatives; that study revealed that sources of variance ("heritability" or "familiality") related to family membership strongly predicted individual differences in plasma peptides (Rubin et al. 2014). Antibody-based assays provide an index of hormone levels, but do not precisely describe the molecular concentrations of a given peptide. In addition, the degree to which peptides are biologically available may vary considerably, especially if samples are first "extracted" using other chemical or physical procedures. There is new evidence from a more exact quantitative method, mass spectrometry, indicating that the levels of oxytocin and vasopressin in blood are much higher than previously assumed, probably because peptides are sequestered on common proteins such as albumin (Martin and Carter 2013), and thus removed and discarded by extraction. Other binding proteins, including the neurophysins, which are synthesized in conjunction with oxytocin and vasopressin also may have a role in determining the functional effects of these peptides. Even within blood samples studied *ex vivo,* the functional dynamics of peptide remain incompletely described (Martin and Carter 2013).

Functional sources and targets for hormones are difficult to specify. Many fundamental questions have not been successfully addressed. For example, what are the sources of functional and behaviorally-active peptides? Outside the brain, oxytocin-synthesizing cells have been identified in a variety of tissues, including the heart, skeletal muscle, enteric nervous system, pancreas, the adrenal medulla, thymus, gonads and placenta. Are the oxytocin and vasopressin levels measured in bodily fluids, including the plasma and saliva derived primarily from the hypothalamus via the posterior pituitary or do these somatic sources also contribute significantly, with consequences for behavior? If peripheral sources of peptides do contribute to behavior, what regulatory mechanisms guide this process and do they differ depending on gender, age or social context? What role do sensory afferents and the autonomic nervous system play as we seek to understand the brain-body interface and the functions of these neuropeptides in the development of affiliative or defensive behaviors?

Individual and sex differences and context. Every individual has a different set of genes and a different life history. Even in identical twins experience and epigenetic variation can alter gene expression, and eventually physiology and behavior. Genetics and epigenetics contribute to these. In the context of the physiology of both positive social behaviors and aggression there is increasing evidence for sex differences. Theorizing about sex differences has been focused historically on the actions of sex steroids. However, sex differences also exist in oxytocin and vasopressin pathways, the origins of which are not fully understood. Male-female differences are particularly apparent in response to early life experiences and in the face of severe challenge or trauma in later life (Carter 2007; Carter et al. 2009). The consequences of a given peptide hormone also may be context dependent (Bartz et al, 2011; van IJzendoorn and Bakersman-Kranenberg, this volume). In turn, context and experience interact with genetics and gender. Comparisons of males and females, in the context of individual differences in life history, will be necessary to permit a sophisticated analysis of the biological and developmental foundations of both peace and war.

The value of animal models. Physiological responses in modern humans are the consequence of evolution acting upon biological and neural substrates, some of which are shared across species. Thus, cross-species comparisons can inform our understanding of physiological mechanisms underlying positive or negative experiences. However, social and physiological systems differ among species. Some animal models may be more relevant than others because they share with humans evolved social systems or behavioral traits, such as the capacity to form lasting social relationships and dependence on others (Carter et al. 1995; Carter 2014). As one example, socially monogamous prairie voles share with humans a reliance on social interactions, as well as the capacity to form life-long social bonds, exhibit biparental and alloparental care of the young, produce high levels of oxytocin, and maintain high levels of parasympathetic activity (Carter et al. 2009). Studies focusing on the capacity for social relationships, and on neural systems [such as the autonomic nervous system (Porges 2011) and oxytocin and vasopressin] that are shared among mammals are offering powerful insights into the neurobiology of social behavior (Hostinar et al. 2013).

Neurotransmitter-peptide interactions. Among other critical elements in the emerging biochemistry of socioemotional states are peptide interactions with systems involving dopamine, serotonin (van IJzendoorn and Bakersman-Kranenburg, this volume) and inhibitory neurotransmitters such as GABA. As one recent example from animal models, GABA plays a critical role in behavioral regulation. Furthermore, the development of the GABA system has been shown to be sexually dimorphic. The maturation of the GABA system is influenced by the presence or absence of oxytocin at the time of birth, with consequences for social and emotional behaviors in later life (Tyzio et al. 2006; 2014). In addition, GABA is involved in the communication among brainstem nuclei involved in autonomic regulation, especially through vagal pathways (Wang et al. 2002). Although beyond the scope of this review, studies of these interactions will be important to the future understanding of the capacity for peace.

Peptide interactions are expected. Oxytocin and vasopressin systems have dynamic functional interactions with each other (Carter 1998; Neumann and Landgraf 2012). What is the nature of these interactions? Is it valid to study only one of these processes at a time? Does the relationship between oxytocin and vasopressin vary during sensitive periods of psychosocial development, in the face of environmental challenges, context, or between the sexes? The features of these interactions are poorly understood especially in humans. It is possible that interactions between these two peptides help to explain the capacity of oxytocin to have "paradoxical" behavioral consequences, including both positive and negative behavioral outcomes (Bethlehem et al. 2014; Weisman and Feldman 2014).

Sensitive periods may be epigenetic and interact with sex. There is increasing evidence that experiences, especially in early life can have lasting behavioral and epigenetic consequences (Champagne, 2012; Zhang et al. 2013). Developmental periods including gestation, infancy and childhood, contain sensitive periods for tuning emotional and social behaviors. The very act of being born, which may take on many forms, is epigenetic. However, manipulations of endogenous and exogenous oxytocin are routine during birth, with largely unknown consequences for later physiology and behavior (Carter et al. 2009). The nature of the molecular processes associated with experience-associated changes in behavior are only now becoming apparent and many questions remain.

Modeling human experiences. Recently, the Mother Child Education Foundation (Anne Çocuk Eğitim Vakfı), based in Turkey, suggested that family- and community-based programs designed to enhance early child development can alter patterns of decision making within the families and communities, so that there is greater "peace" and less conflict within families as well as within the larger community. The identification of physiological substrates, such as peptide pathways, associated with different patterns of social organization may generate data relevant to the physiological basis of these differences in sociality. However, the extrapolation from biological studies to constructs derived from human cognition is difficult. For example, do the behavioral states or experiences described as "social behavior" in animals correspond to broad human constructs such as "peace" or "love" (Carter and Porges 2013)? There is increasing evidence that oxytocin acts on neural substrates necessary for a sense of safety (Porges 2011). In the search for the biological

basis of peace it may be helpful to focus on less anthropomorphic constructs, perhaps using terms such as emotional or physical “safety”? Oxytocin may have a context-dependent capacity to serve as a kind of physiological metaphor for “safety” (Carter 2014). Humans are capable of experiencing a sense of purpose, in some cases showing acts of bravery or self-sacrifice. In the context of individual survival such behaviors appear “irrational.” Perhaps the novel behavioral effects of peptide hormones may help to explain not only our capacity for reproduction and life, but also our capacity to face death with valor. Could the surges of oxytocin which allow women to survive the trauma of birth, also allow humans to die with a sense of peace and safety? Do changes in or individual differences in peptide pathways help to explain the individual phenomenology and time course of responses to trauma (Olff et al. 2013; Seng et al. 2013; Feldman et al. 2014)?

The Promise of Formative Childhood.

Specific pathways, involving oxytocin and other biochemical systems, can influence the expression of behavioral states that would support social structures associated with peace. Peptide pathways are active across the lifespan. However, the developmental effects of peptides are of particular importance to individual and sex differences in temperament and to the capacity for peace. Early nurturing can alter human behavior through formative and epigenetic effects on peptide pathways. Uncovering the deeper biology of these pathways can offer a fresh perspective on the role of formative childhoods in human behavior. Although we are in the early days of the search for a science of peace, we propose here that the evidence is strong that the most efficient and enduring routes to peace are through formative childhoods.

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