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CHAPTER 14

The Roots of Compassion: An Evolutionary and Neurobiological Perspective

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Abstract

Compassion for others and social support have survival value and health benefits. Although compassion is sometimes considered uniquely human, critical components of compassion have been described in nonhuman mammals. Studies originally conducted in social mammals and now in humans have implicated neuropeptide hormones, especially oxytocin, in social cognition, a sense of safety, and the capacity of sociality to permit compassionate responses. In contrast, the related peptide vasopressin and its receptor may be necessary for forming selective relationships and for the apparently paradoxical effects of oxytocin, which can include increases in fear and avoidance. Oxytocin and vasopressin may contribute to sex differences in compassion. Furthermore, among the processes through which oxytocin and vasopressin influence behavior and health are complex effects on the autonomic nervous system. Knowledge of the mechanisms underlying the benefits of compassion offers new insights into the healing power of positive social behaviors and social support.

Key Words: compassion, helping behavior, oxytocin, vasopressin, autonomic nervous system, sex differences, evolution, neurobiology

Overview

This chapter reviews neurobiological mechanisms implicated in compassion through the lens of evolution. While defense behaviors are typically viewed as having a critical role in survival and reproduction, the evolutionary benefits of prosocial behaviors, including compassion for the suffering of others, are not as widely recognized. Yet prosociality is a primary component of social behavior among many species, and it has many advantages for groups and individuals. A sense of caring for others can have beneficial emotional, intellectual, and health consequences. Groups in which individuals act for the benefit of others are more likely to thrive. These effects may extend from the individual to society in general, and knowledge of these systems holds relevance for the survival of our species.

Compassion is sometimes considered uniquely human (Adolphs, 2006). Indeed, humans have complex cognitive processes and the ability to take the perspective of others (Lamm et al., 2008; Decety & Porges, 2011). Embedded in these processes is a sophisticated capacity for compassion, including witnessing or attempting to alleviate the pain of others. However, components of compassion also exist in nonhuman species, and research in other mammals helps us understand the neurobiological substrates of compassion. Here, we conceptualize compassion as an effective mechanism to motivate helping behavior in humans, and argue that a simple form of compassion may drive helping in other species as well. As evidence of the universality of positive social behaviors that resemble compassion, we provide a specific case of helping behavior in rats.

Recent evidence suggests that mammalian neuropeptides, including oxytocin and the related peptide vasopressin, play a central role in the capacity for and expression of social traits and emotions. Primitive molecules that are essential to life on

earth are used and reused in many biological contexts, ranging from the union of hormones with receptors, through to complex societal and cultural practices. Understanding the neurobiology of oxytocin and vasopressin and their receptors also may help refine and more accurately predict individual differences in the outcome of attempts to study or enhance compassion.

Definitions of Compassion

Compassion is defined in this volume as "sensitivity to the pain or suffering of another, coupled with a deep desire to alleviate that suffering" (Goetz, Keltner, & Simon-Thomas, 2010). If compassion is operationally defined to include contingent social responses to emotional expressions of pain, fear, or hunger (such as isolation calls and hunger cries), then components of these, such as approach, consolation, and helping behaviors, are detected in the repertoire of many vertebrates, ranging from primates to rodents.

Compassion and the related concept of empathy are usually presented as psychological constructs, describing feelings, expressions, and behaviors that enable individuals to recognize, perceive, and respond appropriately to the emotional states of others. There is now a converging agreement that compassion and empathy involve complex socioemotional competencies. For example, empathy encompasses different components, including empathic arousal and empathic concern (Decety et al., 2012). *Empathic arousal*, which refers to the unconscious contagious sharing of affect, is the first building block of empathy to appear during ontogeny (Decety & Michalska, 2010; Michalska et al., 2013; Roth-Hanania et al., 2011). In turn, individual levels of compassion and empathy may be associated with individual differences in arousal experienced while viewing others in physical distress. It is also possible to use a combination of psychophysiological and behavioral measures to differentiate constructs such as arousal and concern from each other. In the analysis of compassion, issues and techniques similar to those studied in empathy may apply.

Social Behaviors, Including Compassion, Are Evolved Traits

The powerful consequences of the presence or absence of others are seen as shaping forces in evolution. Social interactions and within-species interdependence are universal components of life on earth. Even single-cell bacteria are more reproductively successful in the presence of others of their own species. The sophisticated expression of, or full experience of, compassion depends on cognitive processes and cortical capacities that are unique to humans. However, behaviors resembling compassion, empathy, and consolation have been described in other social species as diverse as bonobo chimpanzees (Preston & de Waal, 2002), domestic rats (Ben-Ami et al., 2011), and prairie voles (Burkett et al., 2016).

The basic neurobiological elements necessary for compassion, and other forms of sociality, exist in some rudimentary form in many species. The neocortex, which varies widely among species and individuals, is not the sole source of social cognition. Processes that rely on the more conserved brainstem and autonomic nervous system are essential to prosociality. Furthermore, the affective experiences associated with positive sociality and helping may be major motivators of rewards for prosocial behaviors in non-human animals.

Mammalian Reproduction as an Evolutionary Prototype for Compassion

As mammals evolved, they became increasingly dependent on social cues and social support from others, usually of their own species. Social behaviors allowed mammals to more safely eat, digest, sleep, mate, and care for their dependent young. The processes that led to the evolution of mammalian social engagement and communication, and in some species compassion, were associated with the evolution of the neurobiology of the central and autonomic nervous systems (Porges, 2011; Porges, this volume).

The neural substrates of emotions are shared across many species (MacLean, 1990). These same systems are involved in various aspects of reproduction, including social contacts and preferences, sexual behavior, and the basic biology of motherhood. Young altricial mammals depend on their mothers for prenatal and postnatal nourishment. The postnatal interaction between mother and infant involves highly conserved patterns of physiology and behavior that may serve as prototypes for mammalian sociality. The circuits involved offer the potential for selective responding to individuals of the species, such as a mother to her offspring, which probably did not exist in the reptilian ancestors of modern mammals. Furthermore, most humans not only are attracted to babies in general, but also may become quickly and selectively emotionally bonded to their own baby. Behavioral and emotional selectivity, which are essential to social bonds

and mothering, also may be in some cases features of human compassion.

Helping Behavior in Nonhuman Animals

Prosocial actions meant to benefit others are adaptive and are found across multiple taxa and species. As specific evidence of the evolved nature of the response to distress in others, we offer the following examples. For instance, research shows that ants will help other ants by releasing them from a foot-snare (Nowbahari et al., 2009). Chimps will help a human experimenter retrieve an object that is out of reach (Warneken & Tomasello, 2006), and demonstrate targeted helping (Yamamoto et al., 2012). Bonobos show consolation behavior in response to signs of distress from others (Clay & de Waal, 2013). Elephants (Lee et al., 2016) and hyenas (Owens & Owens, 1984) show non-parental care of young. Bats share food with disabled conspecifics, despite little chance of receiving anything in return (Wilkinson, 1984). Ravens delay eating in order to alert others to the location of food (Heinrich & Marzluff, 1995). Many other instances of helping, communal nesting, and allomothering have been documented (Ben-Ami et al., 2014; Dugatkin, 1997).

In humans as well as other mammals, an affective response to another's distress can motivate prosocial behavior. Humans and other mammals can experience the pain and distress of others as aversive. This affective experience is a crucial component of helping to motivate the desire to end the distress of others. Affective resonance, particularly the transfer of distress between individuals, exists in many nonhuman animals, and can be thought of as a basic form of empathic arousal. As described later, a growing body of evidence points to shared biological elements for compassionate arousal in human and rodents, including homologous brain regions, and the autonomic and endocrine mechanisms (Panksepp & Panksepp, 2013). Moreover, as in humans, the expression of helping behavior in rodents is higher in females and stronger for familiar others versus strangers (Decety et al., 2016). Thus, it is not unreasonable to posit that emotional arousal experienced in response to another's distress can motivate animals to help a conspecific.

Helping behavior has been demonstrated in laboratory rodents. For example, rats will refrain from pressing a lever that shocks a conspecific, press a lever to relieve a rat dangling in midair, reciprocate food sharing, prefer mutual reward to selfish reward, and release a cage mate trapped inside a restrainer in a paradigm termed the "helping behavior test" (Decety et al., 2016). For this test, rats are exposed to a trapped conspecific for daily, one-hour sessions. The restrainer has a door that could be opened from the outside, by the observer rat alone. The trapped rats are not in physical pain and are able to turn around inside the restrainer, yet they typically try to escape the restrainer and appear to experience distress. The free rats exposed to a trapped conspecific demonstrate a movement pattern consisting of repeated approaches to the trapped rat, touching the trapped rat with their snout through holes in the restrainer, digging and biting at the restrainer, and attempting to reach the trapped rat. When tested with trapped cage mates, rats were motivated to end the distress of the trapped cage mate, and learned to open the restrainer in about five sessions. The behavior may first occur accidentally, but it becomes intentional, as is evidenced by the use of a consistent method for opening the restrainer, with short latency, and a delay in the freezing initially caused by the door falling over. The opener rats also manifested increased activity in the minutes following door-opening, and often urinated on the restrainer door, an apparent expression of dominance. Once rats learned how to open the restrainer, they did so quickly and intentionally in following sessions. This suggests that door-opening is reinforcing. Rats do not open an empty restrainer or one containing a toy rat, indicating that the presence of the trapped rat, rather than the restrainer itself, is the motivator for door-opening.

Rodents are highly social animals, and, like humans, rats find social interaction rewarding; thus a possible motivation for releasing the trapped rat is to gain social contact. To test this hypothesis, the researchers checked to determine whether rats would still help a cage mate if contact after door-opening was prevented. They found that contact was not necessary for the helping behavior observed in this paradigm. When rats were released into a separate arena after door-opening, helping continued for a period of several months, until testing had to be interrupted. Only by removing the trapped rat could door-opening behavior be extinguished. Furthermore, when helping was pitted against access to chocolate chips, rats demonstrated helping behavior and on the majority of trials, shared the chocolate with the trapped rat.

While arousal, possibly a negative affective response to another's distress, is a critical component for rats' helping behavior (Ben-Ami et al., 2016), it is possible that helping is rewarding for

the rats, not merely because it extinguishes a negative stimulus. Other social behaviors in rodents have been shown to be dependent on brain regions involved in reward (Dolen et al., 2013; Gunaydin et al., 2014).

These experiments show that rats find releasing a trapped cage mate a rewarding act, and that they are motivated to repeatedly help, intentionally and quickly, over many days, with no previous training, external reward, or observable benefit to themselves. Yet all of these experiments were conducted on cage mate pairs, who were highly familiar with each other and returned to the same cage following testing. The researchers wanted to know how rats would interact with strangers, and others who were different from them.

One of the most defining aspects of motivated helping in humans is the bias for in-group members. We are more motivated to help others from our own group. There is not much known about the biological basis for this behavior. To test how helpful rats would be in different social situations, the experimenters tested rats with trapped strangers, and found that rats were as helpful to strangers as they were to cage mates. Yet these rats were all from the same Sprague-Dawley strain, meaning they are nearly genetically identical. So, the next experiment tested rats with cage mates and strangers of a different strain, the black-caped Long-Evans rats. While rats were motivated to release cage mates and strangers of their own strain, they did not open the restrainer for rats from another strain, with whom they were unfamiliar. But cage mates, rats who were housed with a rat of the other strain, treated that rat as they did their own strain (Ben-Ami et al., 2014). Importantly, rats then generalized this behavior, releasing strangers of the other strain. This shows that prosocial motivation is flexible in rats and can be modified by social experience.

The finding that rats can learn to help others of another strain was encouraging and led to the idea that prosocial motivation is actually determined by social experience, not genetic relatedness, as is sometimes posited. To test if there is an inherent biological imperative to help genetically similar others, rat pups were cross-fostered to mothers from another strain at birth, and raised to adulthood never meeting members of their own strain. If rats possess some hard-wired knowledge of genetic similarity to others, they would be expected to help others of their own strain as adults, even lacking any social experience with their strain. Yet, when the fostered rats were tested with trapped strangers of their own strain as adults, they failed to release them. They preferred instead to help their adoptive strain. From this surprising finding, we learn that the biological identity has no power to induce prosocial motivation in rats; rather, it is the positive social experience acquired with other animals that leads them to help those they know, and their group members. It is important to note that prosocial motivation and identity are not one and the same. Rats are capable of distinguishing the different strains, as is evidenced by their capacity to generalize to one strain and not the other.

In conclusion, as has been demonstrated for humans and other animals, prosocial motivation in rats depends on the social context. Social animals, including rats, demonstrate social memory and are able to distinguish between individual conspecifics. The social classification of conspecifics, as familiar others or in-group members, determines the affective response to their distress and prosocial motivation (Ben-Ami et al., 2014).

Studies of this kind leave no doubt that nonhuman animals, as well as most humans, can sense and respond to the emotions or experiences of others. It is interesting to consider whether these experiences are truly homologous to those that humans describe or experience as compassion or empathy. Homology among these experiences may be examined, in part, by understanding the evolution of, and biological mechanisms underlying, these behaviors.

Oxytocin and Vasopressin: Building Blocks for Sociality and Bonding

Research on the evolved origins of compassion, and also empathy, has directed attention toward the neuropeptides, especially oxytocin and vasopressin. These molecular and genetic building blocks for sociality predate the evolution of modern vertebrates by an estimated 700 million years (Acher et al., 1995). Both oxytocin and vasopressin evolved from a single peptide, vasotocin, thought to have primary functions in water balance. Highly chemically reactive elements, such as the sulfur bonds found in oxytocin and vasopressin, give these molecules exceptionally broad functions. The chemistry of the amino acids that compose oxytocin and vasopressin allow them to be attracted to and attach to each other and to other substrates, including compounds in blood and specific receptors in tissues throughout the brain and body (Martin, Davis, & Carter, unpublished data). Thus, the metaphor of

"bonding" extends from the simple to the complex, and from molecules to molar components of behavior.

Molecules generated by ancient genes related to oxytocin and vasopressin have been implicated in social and sexual behavior in the tiny hermaphroditic nematode *C. elegans* (Garrison et al., 2012), although "sociality" in worms is not likely to involve emotional states that correspond to human social experiences. Studies in invertebrates suggest the broad involvement of neuropeptides in sociality across many unrelated species and supports the primitive nature of these processes.

Oxytocin is particularly important to mammals because it facilitates mammalian sexual behavior, birth, lactation, maternal behaviors, and social bonds (Marlin et al., 2015; Beery et al., 2016; Carter et al., 1995). Oxytocin facilitates the birth process through powerful muscle contractions. Concurrently, oxytocin protects the fetal nervous system during the stress of birth (Tyzio et al., 2006). Oxytocin also facilitates milk ejection and thus lactation. Lactation and postnatal nurture, in turn, allow the birth of comparatively immature infants. Milk also contains hormones and regulatory factors and facilitates postnatal intellectual development in offspring. Oxytocin and vasopressin may be especially important in early life, but they also act across the lifespan to integrate various processes such as social bonding, emotional feelings and responses, and the functions of the autonomic nervous system. Oxytocin, in particular, seems a likely component of various forms of prosociality, including compassion.

The actions of oxytocin and vasopressin depend on the availability of their receptors. Individual and species differences in peptide receptors probably play an important role in individual differences in sociality and social communication. Thus, as the capacity to assess both peptides and their receptors increases, we will gain a deeper understanding of the role of oxytocin and vasopressin in the behavioral states and responses necessary for individual differences in compassion.

Oxytocin sits at the center of a neuroendocrine network that coordinates social behaviors and concurrent responses to various stressors, generally acting to regulate reactivity to stressors (Carter & Altemus, 1997; Carter, 1998). Oxytocin tends to decrease fear and anxiety and to increase tolerance for stressful stimuli. Oxytocin may protect the vulnerable mammalian nervous system from regressing into the primitive states, such as the "reptile-like" freezing pattern, which is based on lower brainstem activity, with an associated shutdown of higher neural processes. Mammals—with their comparatively large cortexes and a corresponding need for high levels of oxygen—cannot endure long periods of hypoxia. Thus, the capacity of oxytocin to protect against shutting-down processes, including hypoxia, is fundamental to survival. At the same time, oxytocin appears to encourage various forms of sociality (Carter, 2014), especially those, such as mothering and sexual behavior, that require intimacy and immobility without fear (Porges, 1998). Oxytocin acts on pathways that include both the central and autonomic nervous systems, and may even allow neural systems that were previously involved in defensive functions or basic metabolic processes to be coopted for prosocial actions. For example, in compassionate states, the presence of oxytocin might reduce emotional and autonomic over-reactivity, thus permitting individuals to witness the suffering of others without necessarily experiencing high levels of personal distress. Thus, oxytocin may permit compassion while maintaining the capacity of the observer to engage in helping behaviors or other adaptive responses.

When oxytocin is released, it works in conjunction with vasopressin. Vasopressin is structurally similar to oxytocin, differing by only two of nine amino acids. Vasopressin has important physiological functions in the regulation of water balance, blood pressure, and autonomic functions. Behaviorally, vasopressin is most often implicated in active protective or defensive behaviors, including territoriality and aggression, and is probably critical to the selective sociality that characterizes social bonds (Carter, 1998). The actions of vasopressin may allow selective engagement and selective forms of compassion that require active responses. Alternatively, stimulation of the vasopressin receptor might act to inhibit compassion toward strangers.

Whether vasopressin plays a direct role in compassion remains to be explored. However, because of the structural similarity of the oxytocin and vasopressin molecules, these peptides can potentially influence each other's receptors. The functions of oxytocin and vasopressin are often—but not always—in opposite directions. While chronic exposure to oxytocin tends to reduce behavioral and autonomic reactivity to stressful experiences, in contrast, vasopressin is associated with arousal, mobilization, and vigilance. Vasopressin also plays a role in social behaviors and has adaptive functions in the regulation of the

hypothalamic-pituitary-adrenal (HPA) axis, especially in the face of behavioral and physiological stressors.

Dynamic interactions between oxytocin and vasopressin are important to the approach and avoidance components of sociality. In men, intranasal oxytocin facilitates "trust" behavior, as measured in a computer game (Kosfeld et al., 2005), and the ability to detect subtle cues from pictures of eyes (Lischke et al., 2012). A growing literature suggests that many aspects of sociality, including the salience of social cues (Shamay-Tsoory & Abu-Akel, 2016), can be modulated by these peptides. In this manner, peptides may have direct and indirect effects on compassion.

Receptor Dynamics Can Help Explain the Behavioral Actions of Oxytocin and Vasopressin

Oxytocin and vasopressin are synthesized in, and are particularly abundant in, the hypothalamus, but to function, they often must reach distant receptors, including those in the cortex and in lower brain stem areas and other systems responsible for autonomic functions. Oxytocin was historically assumed to have only one receptor. The oxytocin peptide uses the same receptor for many functions throughout the body, including the nervous system, reproductive tract, and immune and digestive systems. Oxytocin receptors throughout the body, such as the heart or digestive system, also play a role in providing oxygen and energy needed for many adaptive functions; these in turn are necessary for responding to and helping others. This feature of oxytocin may allow coordinated effects on behavior and physiology. These properties of oxytocin also can play a role in the integration of behavioral and emotional responses in the face of challenges to others (Grinevich et al., 2016).

Vasopressin has three subtypes of receptors. Of these, the V1a receptor is abundant in the brain and cardiovascular system, and it is implicated in various kinds of social and defensive behaviors, as well as blood pressure and local fluid regulation. A second vasopressin receptor, V1b, plays a role in the regulation of pituitary responses to stress and may affect aggression and maternal defense (Bayerl et al., 2015). The V2 vasopressin receptor is found in the kidney and plays a critical role in water balance. In comparison to oxytocin, vasopressin is thought to be the more primitive molecule, with homeostatic effects that integrate behavior with the physical environment. But both molecules probably have been coopted for many adaptive functions.

The distributions of oxytocin and vasopressin and their receptors vary across species, from voles to primates (Witt et al., 1991; Freeman et al., 2014), and in humans are likely to be highly heritable. However, the expression of these peptide receptors also can be regulated epigenetically (Gregory et al., 2009), allowing experience to modulate the availability of receptors for these peptides and thus increase or decrease their capacity to affect adaptive responses across the lifespan.

The behavioral effects of oxytocin and vasopressin are the result of actions on both the oxytocin and vasopressin receptors, and these effects may be sexually dimorphic (Carter, 2007; Albers, 2015). Variations in the gene for the oxytocin receptor (*OXTR*) and vasopressin receptors have been repeatedly associated with social behaviors. Beginning with early studies conducted in autism, genetic variation in the *OXTR* gene was associated with social deficits (Jacob et al., 2007), a finding that was replicated in studies of tendencies toward empathy, and now a broad range of social behaviors (Feldman et al., 2016). Among these studies in autism and other conditions, it is common to find genetic variations that may be indexed by single-nucleotide polymorphisms (SNPs) in the gene for the oxytocin receptor (for example, rs53576) (Rodrigues et al., 2009). This is only one example, since variations in the *OXTR* gene also have been related to behavioral outcomes. The interpretation of these studies is complicated by the fact that most studies are small and methodologies are extremely variable. Furthermore, the gender of the subject showing compassion, and to which compassion is directed, can interact with genetic variations in the *OXTR*, even when oxytocin is administered as an intranasal spray (Palgi et al., 2016).

In spite of these concerns, as these studies have accumulated, some patterns are emerging. For example, individuals who are very sensitive to the social environment may have a particular genetic pattern of SNPs in the *OXTR*, while those who are less sensitive may have a different genetic background in oxytocin pathways. Our ongoing research in prairie voles supports the hypothesis that epigenetic changes, due to early life experiences, such as exposure to differential parenting or trauma, could play a role in individual differences in these peptide receptors (Carter et al., 2009; Bartz et al., 2015), and thus in the actions of oxytocin and vasopressin. Therefore, variations

in the capacity for compassion can be supported by a variety of mechanisms, including, but not limited to, individual differences in oxytocin and vasopressin and their receptors.

The Autonomic Nervous System is Critical for the Social and Emotional Functions of Oxytocin and Vasopressin

The autonomic nervous system is a bidirectional system, including sensory and motor components, and plays a critical role in both the expression and experience of emotional states. In a general sense, responses and adaptations in the autonomic nervous system are fundamental to the processes that underlie compassion, including affective experience, emotional expression, facial gestures, vocal communication, and contingent social behaviors. Refined neural pathways support the needs of mammalian communication and selective sociality.

Brain stem structures involved in the regulation of autonomic state are sentries of visceral states and feelings, and they can convey defensive signals, including emotional cues, to the periphery. The brain stem also provides a portal through which sensory information related to peripheral sensations, including social cues, contributes to the general activation of higher brain structures, including the cortex. Thus, visceral regulation can be mediated by brain stem systems that control the heart and gut and also can convey sensory information to the brain stem. Brain stem structures, in turn, transmit information to brain regions, including cortical regions, that regulate the autonomic state (Critchley et al., 2004).

The mammalian nervous system must be able to sense danger and transition quickly between positive social behaviors, such as those seen in parenting, and responses to life-threat. The neural circuits for self-defense regulate fight/flight behaviors and, in more extreme situations, freezing or shutdown responses. These behavioral strategies are supported by the brain stem and a complex bidirectional network of autonomic nerves, which coordinates behavioral demands with physiological and visceral processes, including heart rate, respiration, and metabolism.

Compassion may be described as a "gut feeling." Visceral sensations, in turn, represent the communication between visceral organs (e.g., heart and gut) and the brain stem, through the autonomic nervous system. However, the emotional feelings associated with compassion may overcome states of fear and promote social communication and engagement.

What we experience as states, emotions, and behavioral traits in ourselves, and what we perceive in others, require activity in archaic brain stem and autonomic processes, which predate and may override the activities of the modern cortex. Basic to survival is the capacity to react to challenges or stressors and maintain visceral homeostatic states necessary for vital processes, such as oxygenation of tissues and the supply of nutrients to the body. For these reasons, the neural circuits involved in regulating social interactions, and feelings such as compassion, would be expected to overlap with autonomic processes regulating visceral homeostasis.

The Parasympathetic Nervous System and Vagus Nerve are Central to Sociality

Of particular importance to emotional regulation and social engagement is the vagus (10th cranial nerve) (Porges, 2011; Porges, this volume). The mammalian version of the parasympathetic system includes both a dorsal vagal motor process (which is ancient and found throughout vertebrates) and a newer ventral vagal efferent (also motor) pathway, of particular importance to mammalian social communication. This vagal system has a major role in parasympathetic function, and both afferent and efferent vagal pathways regulate social engagement and social communication. The ventral vagal pathway provides a neuroanatomical and neurophysiological link between the brain stem regulation of the striated muscles of the face and the regulation of the autonomic nervous system (Porges, this volume). The parasympathetic nervous system and the autonomic processes that it regulates are necessary to support physiological states and feelings such as those necessary for compassion.

Oxytocin and vasopressin receptors are abundant both centrally and on peripheral organs that are innervated by the vagus, such as the cardiovascular, digestive, and immune systems, thus regulating both motor and sensory processes. Visceral feedback from these systems may be experienced as either positive or negative emotions. These experiences are filtered through central nervous system pathways that contain receptors for both oxytocin and vasopressin. Thus, the visceral nervous system—regulated in part by oxytocin and vasopressin—has a plausible role in various emotions, including those associated with compassion.

The Autonomic Processes and Ancient Brain Systems May Take Precedence Over Cognition

When we examine human constructs such as compassion in existing life forms, we are seeing

the expression of neural and biochemical processes that played a major role in the successful evolution of mammals, and eventually the human species (Carter, 2014). As we attempt to deconstruct emotions or feelings, including compassion, it is helpful to be aware that our nervous system is largely wired from the "bottom up." A rational desire to show or experience compassion may be preempted by processes associated with self-preservation or survival. However, higher brain structures and manipulations of state, such as those involved in contemplative practices, can modulate lower brain stem functions. For example, meditation and breathing exercises may allow a shift from fear or anger to states more compatible with compassion (Porges, this volume).

Critical to understanding concepts such as compassion is an awareness of the capacity of the nervous system to detect and evaluate the positive and negative features of the social environment. Thus, the processes that regulate approach or avoidance are basic to sociality in general. Sensory, autonomic, emotional, and motor systems can be primed to allow an individual to detect and interpret the features of social cues, and then to respond with appropriate motor and autonomic reactions. All of these are sensitive to peptides, including oxytocin and vasopressin. For example, the capacity of peptides such as oxytocin to dampen emotional reactivity could be critical to the ability of an individual to reduce over-arousal or defensive behaviors, and show compassion in the face of suffering in others.

The Comparative Neurobiology of Positive Sociality

One approach to understanding the neural mechanisms underlying prosocial behaviors, and substrates for compassion, has been to examine interspecies differences in sociality among mammals (Carter et al., 1995). Socially monogamous rodents, such as prairie voles, are especially sensitive to their social environment and offer a useful model for understanding the neuroendocrine mechanisms that enable positive social experiences. Studies of social bond formation in prairie voles have been particularly helpful for understanding the effects of oxytocin. The importance of social interactions can be understood in part by examining the consequences of placing animals in social isolation. For example, prolonged isolation is associated with increases in oxytocin in females. Elevated oxytocin in this context may be protective against the negative consequences of isolation. It is possible that this increase in oxytocin would, in turn, increase tendencies toward subsequent sociality. There also is evidence that opioids and dopamine, probably through interactions with oxytocin and vasopressin, influence social behavior and specifically social bonds (Aragona et al., 2006). Social interactions have powerful effects on reward systems, possibly contributing to the emotional effects associated with compassionate responses. Based on the well-documented actions of these molecules, this same suite of hormones and neurotransmitters also may influence the detection of, or response to, the pain or suffering in others, while reinforcing the rewarding feelings associated with helping others.

Prairie voles also have a human-like autonomic nervous system, characterized by high levels of vagal efferent activity through the myelinated, ventral vagal pathways that regulate the heart. Highly social mammals like prairie voles serve as models for understanding the role of the autonomic nervous system and visceral reactions in social behavior. Consistent with this expectation, in prairie voles, social isolation produces profound reductions in vagal control of the heart, increases in sympathetic arousal, and a reduced capacity to recover after a stressor. Oxytocin injections can reverse the cardiac effects of isolation (Grippo et al., 2009). Behavioral responses of prairie voles to the distress of others have been documented. These behavioral responses were prevented by blocking oxytocin receptors, thus implicating oxytocin in what could be argued is a form of "compassion" or empathy (Burkett et al., 2016).

Oxytocin and vasopressin receptors are found in many limbic structures, including the extended amygdala, the bed nucleus of the stria terminalis (BNST), and the lateral septum. The amygdala and its connections serve a role in the integration of reactions to various kinds of sensory stimuli, including approach and avoidance. In human males, intranasal administration of oxytocin inhibited the activity of the amygdala and altered downstream connections to brain stem structures involved in the regulation of the autonomic nervous system. Vasopressin, acting centrally (in areas including the medial amygdala, BNST, and lateral septum), may elevate vigilance and defensiveness, possibly serving in some cases as an antagonist to the effects of oxytocin (Albers, 2015). Behaviors mediated by the central amygdala may mediate stimulus-specific fear, while the BNST has been implicated in experiences related to anxiety. Other peptides, including corticotrophin-releasing factor (CRF), released during "stressful" experiences

may be anxiogenic, acting in the extended amygdala, including the BNST, to up-regulate responses to dangerous or threatening cues. At least some of the fear-associated or defensive actions of CRF or vasopressin can be counteracted by oxytocin. Thus, oxytocin may have the capacity to reduce fear and calm the sympathetic responses to stressful stimuli.

Sex Differences in Compassion

Sex differences in the actions of oxytocin and the related peptide, vasopressin, are likely to be critical to gender differences in compassion. For example, exogenous oxytocin (given intranasally) can reduce neural activation in the amygdala in men, while in women, the same treatment facilitated activation of the amygdala (Domes et al., 2007). Social stimuli, such as those from an infant, also have neural and behavioral effects that differ between the sexes (Feng et al., 2015a; Feng et al., 2015b). The actions of exogenous vasopressin also are sexually dimorphic (Thompson et al., 2006).

Sex differences in the capacity for or expression of sociality provide hints to the neurobiology of compassion. Females are typically described as more empathic than males (Chakrabarti & Baron-Cohen, 2006). Sex steroids may be involved in this sex difference. Blood levels of oxytocin and vasopressin often do not differ between the sexes. However, both oxytocin and vasopressin are regulated somewhat differently in males and females, possibly due to hormonally dependent differences in both the peptides and their receptors. Of particular relevance to social behavior is evidence that the hypothalamic synthesis of vasopressin is androgen-dependent, in a neural pathway that involves the medial amygdala, BNST, and lateral septum (Albers, 2015). This neural axis is critical to defensive and aggressive behavior, and vasopressin increases in this pathway following developmental exposure to androgens. Peptides acting in this axis, especially on the lateral septum, may create sexually dimorphic vulnerabilities in the capacity to regulate defensive strategies and sensitivity to social cues, which are building blocks for the capacity for compassion. Working in concert, oxytocin and vasopressin allow sexually dimorphic responses to emotionally contradictory tasks, such as forming social bonds or showing compassion, while also permitting rapid behavioral and autonomic reactions, including defensive behaviors or aggression. These and other findings predict sex differences in the substrates for compassion. For example, females in general may be more capable than males of appreciating the suffering of others.

Elevations in oxytocin during periods of isolation also may be sexually dimorphic. In human females, increases in oxytocin were associated with "gaps in social relationships" (Taylor et al., 2006). The significance of isolation-related elevations in oxytocin remains to be empirically determined, but it is likely that oxytocin is a component of a homeostatic, coping process that helps mammals deal with isolation or other stressful experiences. Such responses could also facilitate preparedness for social engagement, a function that might be especially adaptive in females, who may be less able than males to cope with the physical challenges of being alone. In the context of personal safety, the release of oxytocin could encourage social interactions, such as those associated with detecting and responding with compassion to the emotions or experiences of others.

Vasopressin, because of its androgen-dependent occurrence in the extended amygdala and lateral septum, also is a prime candidate for a role in explaining sex differences in social behaviors (Carter, 2007). For example, males and females may experience or respond to compassion-eliciting stimuli using sexually dimorphic neural pathways.

Oxytocin is a likely mediator of compassion, especially if the behavioral reactions involve immobilization without fear and down-regulation of emotional reactivity or aggression, which are essential to several forms of sociality (Porges, 1998). Alternatively, vasopressin might be implicated in situations where a more active or mobilized strategy is required for an adaptive response. Sex differences in the availability or actions of oxytocin and vasopressin and their receptors are important candidates for mediators of sex differences in compassion. However, it is important to keep in mind the fact that these peptide systems can be tuned by experience in early life and also across the lifespan. This tuning process also can be sexually dimorphic, but it introduces additional opportunities for individual variation in compassion across the lifespan. Thus, we could speculate that individual variations in androgens or vasopressin might allow greater variation in the capacity for compassion in males than in females.

Sources of Individual Differences: An Example From Humans

As the study of compassion and related forms of sociality matures, researchers are increasingly exploring individual differences and measuring

biologically relevant outcomes. For example, in one series of studies, college-aged men viewed a mixed martial arts (MMA) video, in which fighters inflict and experience high levels of distress and pain. A series of responses to this MMA video was examined, including the relationship between levels of dispositional empathy, subjective arousal, parasympathetic or vagal status (measured by respiratory sinus arrhythmia; RSA), sympathetic arousal (measured by electrodermal activity), and salivary testosterone (Porges et al., 2015). In a second study, 18–35-year-old men were separated according to whether they carried the rs53576 G or A variant of the *OXTR* (Smith et al., 2014). Individuals with *OXTR* variant rs53576 GG, compared to A allele carriers, showed increased levels of subjective and sympathetic arousal in response to viewing pain in others. GG homozygotes for this gene also expressed greater levels of empathic concern. These findings support the importance of oxytocin receptor variation in emotional and physiological reactions to response to pain experienced by others. Participants with lower parasympathetic activity responded to watching MMA with greater increases in testosterone, suggesting that high parasympathetic tone dampens testosterone reactivity and defensive responding. Findings from this and related studies suggest that individuals with higher baseline vagal tone may be less vulnerable to behavioral and physiological reactivity when confronted with violence. Conversely, low vagal tone is a risk factor for social and emotional regulatory disorders. Individuals with low baseline levels of vagal tone and a concurrent increase in testosterone may be at risk for antisocial and aggressive behaviors, with less capacity to show compassion, especially in the face of emotionally provocative experiences.

The absence of buffering from the parasympathetic nervous system would leave some individuals vulnerable to emotional over-reactivity, either in the face of personal threat or while viewing pain or suffering in others. Especially under conditions of threat or danger, retraction of the "vagal brake" would leave a relative dominance of sympathetic activity; under these conditions, the capacity for compassion might be compromised (Porges, 2011; Porges this volume). In peptide-sensitive individuals (such as those with variant rs53576 GG), especially under conditions of chronic stress, we would hypothesize that oxytocin (through its effects on the brain or autonomic nervous system) could dampen sympathetic and emotional over-reactivity. Whether specific variants in the *OXTR* or factors regulating the expression of the oxytocin receptor are directly regulating vagal activity remains to be examined.

The "Dark Side of Compassion": Do Interactions Between Oxytocin and Vasopressin Influence Responses to Pain or Distress in Others?

The mechanisms through which peptides, including oxytocin, affect behavior have only begun to be considered. However, several recent studies have focused on what has been described as the "dark side" of compassion and also oxytocin. Individuals with high levels of concern for the distress of others may—under some circumstances—elect to punish those who are causing the distress. For example, the tendency of humans to report "in-group" preferences and cooperation, and "out-group" exclusion, increased after treatments with exogenous oxytocin (De Dreu & Kret, 2016).

Both oxytocin and vasopressin are probably involved in the capacity to detect and respond to the emotions of others. However, the emotional responses associated with feeling the pain of others are complex (Bartz et al., 2015; Shamay-Tsoory & Abu-Akel, 2016). For example, feeling the distress of others can lead to attempts to protect those being harmed, or to inflict retribution on those who threaten loved ones. The willingness to experience pain or even death to protect others can contribute to suicidal terrorism and war. This complexity remains poorly understood. For this and other reasons, attempts to use hormones, such as oxytocin, as prophylactic treatments must be approached with caution (Harris & Carter, 2013). However, a deeper understanding of the naturally occurring mechanisms that foster compassion might be facilitated by understanding factors that acutely or chronically enhance the functions of the parasympathetic and oxytocin systems.

Does Variation in Peptide Receptors Explain Species or Individual Differences in Social Behavior?

Explanations for behavioral actions of oxytocin alone are not sufficient to explain the role of oxytocin in social behavior. Evidence for this comes from animal models in which it is possible to inject a peptide and concurrently inactivate or block specific types of receptors. For example, in hamsters, injections of oxytocin can induce flank marking, a form of social communication, through actions on the vasopressin V1a receptor; these effects of oxytocin were seen even when the oxytocin receptor was

blocked, but not when the vasopressin V1a receptor was unavailable (Song et al., 2014). These and comparable studies in other species leave little question that oxytocin and vasopressin engage in "cross-talk" at the level of their receptors (Albers, 2015). Oxytocin and vasopressin may stimulate, and in some cases may directly block, the actions of each other at the receptor level, creating a dynamic system capable of quickly responding to either positive or negative contexts.

Further complicating the translational significance of the role of peptides in human behavior is the ongoing controversy regarding whether the distribution of the oxytocin receptors in Old World primate nervous systems is similar to, or perhaps rather different from, those found in rodents. Oxytocin receptors in primates may not be abundant in limbic system sites predicted by research in rodents; however, oxytocin receptors have been identified in brain regions that also contain high concentrations of cholinergic processes (Freeman et al., 2014). This finding supports the hypothesis that the behavioral actions of oxytocin, especially those related to emotion regulation, may be mediated by effects on the autonomic nervous system. The autonomic nervous system, in turn, is regulated in part by acetylcholine, which in turn regulates various inhibitory processes. The capacity to inhibit fear, while feeling the suffering of others, is likely to be involved in the capacity for compassion.

Vasopressin V1a receptors are abundant throughout the primate brain. As in rodents, at least some of the effects seen following exogenous treatments with oxytocin in humans and other primates may be due to effects on the V1a receptor.

These kinds of dynamic interactions and the complex regulation of peptide receptors preclude a simple interpretation of the actions of oxytocin and vasopressin. However, hundreds of published studies continue to support the importance of the oxytocin and vasopressin molecules in human behavior, including studies of social behaviors relevant to compassion (reviewed by Bartz et al., 2015; Shamay-Tsoory & Abu-Akel, 2016; Feldman et al., 2016).

Variations in genes for both the oxytocin receptor and vasopressin V1a receptors also may moderate the tendency to direct or experience aggression. These relationships probably depend on a variety of intervening variables, including the strength of a relationship with the target for either compassion or retribution (Buffone & Poulin, 2014). For example, one SNP of the *OXTR* (rs53576 GG) is associated with sensitivity to environmental context and specifically associated with empathy, while carriers of the A allele of this SNP seem less sensitive, or even insensitive, to the social environment (Rodrigues et al., 2009; Smith et al., 2014; Feng et al., 2015a; Feldman et al., 2016).

The capacity of oxytocin to affect the vasopressin receptor (Albers, 2015) must be considered in the interpretation of these findings. The behavioral phenotype elicited by vasopressin (or compounds that stimulate the vasopressin receptors) would seem to be a candidate for the defensive behaviors or mobilized responses to threat that are seen in these situations. Conversely, vasopressin might interfere with the capacity for compassion or, alternatively, heighten the tendency toward defense of loved ones who are in distress.

As with other functions of oxytocin and vasopressin, it is unlikely that any single peptide is acting alone to influence emotional reactivity, including those responses that may appear as socially defensive or parochial. In addition, genetic and epigenetic indicators of the status of the oxytocin or vasopressin receptors need to be considered in studies of compassion. For example, blood levels of oxytocin predict brain activation, especially in men and in areas of the prefrontal cortex that have previously been implicated in social sensitivity (Lancaster et al., 2015).

A deeper understanding of the neurobiology and receptor dynamics of oxytocin and vasopressin is particularly important if these hormones are to be administered clinically (Harris & Carter, 2013). Based on the evolved biology of these systems, individual differences are expected. The genetics of the receptors for these peptides seems to be especially variable. Oxytocin and vasopressin and their targets throughout the body also are targets for epigenetic "tuning," allowing modifications of emotional systems by individual experiences.

Can Knowledge of the Neurobiology of Oxytocin and Vasopressin Be Used to Facilitate Compassion?

The most commonly reported consequences of exogenous oxytocin are the enhancement of positive social behaviors and a tendency to improve behavioral responses in various psychopathologies (MacDonald & Feifel, 2013). There is, however, evidence that treatments with exogenous oxytocin can have negative consequences, especially in genetically vulnerable individuals and in psychological contexts associated with threat or fear (Bartz et al.,

2015; De Dreu & Kret, 2016). Men and women may respond differently to what appears to be the same experience. Based on behavioral studies, it has been proposed that these paradoxical effects occur because oxytocin enhances social salience, although mechanisms for this have not been fully articulated (Shamay-Tsoory & Abu-Akel, 2016). At the neuroendocrine level of analysis, we must consider the possibility that the capacity of oxytocin to stimulate vasopressin receptors helps explain individual or situational differences in the response to exogenous hormones. Individual differences in sensitivity are to be expected, based at least in part on variations in receptors, and these could be genetic and epigenetic in origin.

Developmental experiences may be critical to tuning receptor expression and binding. Clues to the origins of individual differences in physiology and behavior can be detected by measurements of hormones in blood, saliva, and other bodily fluids (Carter, 2007). In addition, individual differences in receptors can be indexed through genetic and epigenetic markers. These can be combined with functional imaging and other psychophysiological techniques with, in some cases, an excellent capacity to predict behavior (Porges et al., 2015; Lancaster et al., 2015). A more complete sense of individual responses is possible when measures are taken at several levels of analysis. This work is promising, but still at early stages of development.

Finally, it is increasingly evident that the autonomic nervous system is integral to emotional and social experiences. The autonomic nervous system, and especially patterns of vagal activity, provide indices of individual differences and context-dependent effects of peptides (Bartz et al., 2015). In the face of challenge, knowledge of the resting status of the autonomic nervous system also is capable of predicting later reactions to social stimuli (Porges et al., 2015; Porges, 2011; Porges, this volume). Both oxytocin and vasopressin affect emotional states and traits, in part through autonomic and visceral reactions. Thus, measures of autonomic processes may provide a noninvasive window into the interactive neuroendocrine systems that respond to social cues, providing substrates for the capacity for compassion.

Conclusion

The desire to help others can be elicited by stimuli such as witnessing pain in others. For some, but not all, individuals, these kinds of stimuli have an inherent capacity to induce an autonomic and neural sense of distress, but also a sense of connection. These experiences also may release oxytocin or be sensitive to endogenous oxytocin (Kenkel et al., 2013; Mascaro et al., 2014).

A context of emotional safety also may be relevant to the complex consequences of attempts to use hormones, including oxytocin, to directly influence human social behavior. For example, in healthy individuals, oxytocin may increase a sense of safety. However, there is some evidence that the effects of oxytocin vary according to the emotional history of the individual. Individuals with a history of neglect, abuse, or trauma, and for whom a sense of safety is difficult to achieve, may be at particular risk for adverse reactions following treatment with oxytocin, possibly through the capacity of oxytocin to stimulate the vasopressin receptors (Albers, 2015).

Emotional and visceral states influence how we feel about and react to others, and thus our capacity for compassion. Awareness of factors that regulate emotional responses and feeling leads us to a deeper understanding of the evolved neurobiology of compassion. Selective social behaviors can facilitate survival and reproduction, promoting safety and a sense of emotional security. Sociality is essential to human existence, and it is likely that the neural substrates and hormonal conditions that permit compassion are shared with those that enable other forms of sociality, including willingness to approach or "trust" others, and sensitivity to the emotions or suffering of others. Sensitivity to social cues is one element of compassion. Neural systems, including autonomic functions, that rely on brain stem neuropeptides, such as oxytocin and vasopressin, are plausible candidates in the moderation of these systems.

The strategy of investigating social behaviors by examining the neural systems that rely on oxytocin and vasopressin increasingly has been extended to the level of genetic and epigenetic analysis. For example, individual differences in the genetics and epigenetics of oxytocin and vasopressin receptors have been linked to autistic traits (Jacob et al., 2007), as well as to individual and sex differences in sociality (Feldman et al., 2016) and perceptions of social stimuli (Puglia et al., 2015). Individual or sex differences in the genetics of oxytocin and vasopressin also are associated with individual differences in the capacity for compassion. However, the biological substrates of safety are interwoven with those for defense and reactions to threat or danger. Thus, manipulations of these systems must be done with caution and in a context of safety (Harris & Carter, 2013). Ideally, such studies will also be conducted

with knowledge of individual and gender variations in autonomic function, of other concurrent hormonal processes, and of the sensitivity or expression of receptors that are affected (Smith et al., 2014; Porges et al., 2015).

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