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Toward a Biology of Social Support

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People are, by nature, social animals, and group living is thought to be one of the most significant evolutionary mechanisms by which human beings have survived and thrived (Caporael, 1997). Living in social groups has enabled people to avoid the ill effects of clear physical limitations relative to other species that are larger, have endogenous weapons such as teeth and claws, and have greater mobility and speed. Group living affords collective enterprises such as gathering, hunting, and defense that also facilitate survival.

Researchers in health psychology have discovered another significant and well-established benefit of group living—the health benefits of social contact and social support, particularly during times of stress. In prospective studies controlling for baseline health status, people with a higher quantity and quality of social relationships consistently are shown to be at lower risk of death (Seeman, 1996). In studies of both humans and animals, social isolation is a major risk factor for mortality (House, Landis, & Umberson, 1988). In more than 100 empirical investigations, social support has been tied to reduced health risks of all kinds, affecting both the likelihood of illness initially and the course of recovery among people who are already ill (see Seeman, 1996, for a review). As yet, however, the biological mechanisms underlying the health benefits of social contact and social support are poorly understood, and by the end of this chapter, they will be only modestly clarified. A substantial orchestrated research enterprise will be required to clarify the tantalizing proposed hypotheses, many of which currently draw primarily or entirely on evidence from animal studies.

We begin our analysis with a discussion of early social relationships. Specifically, a close emotional and physical relationship with a caregiver during infancy is believed to be essential for both human and animal development. In addition to the psychological benefits of this relationship, there are important benefits for the development of stress-regulatory systems whose dysfunctions are implicated in many diseases and disorders. We focus on the physiological and neuroendocrine effects of the presence of attachment figures on offspring responses to stress and speculate about the mechanisms whereby these early relationships may permanently affect health across the life span. We then address early experiences of separation and separation distress in animals and humans and their physiological and neuroendocrine concomitants. We next ex-

amine the literature implicating neuroendocrine mechanisms, especially oxytocin and endogenous opioid peptides, as being potentially central to the psychological and physical benefits observed in the social support literature. We also address the possible roles of other neurohormones in these phenomena, for which information is less plentiful, including vasopressin, norepinephrine, and serotonin (Nelson & Panksepp, 1998). We end with hypotheses about the protective and health-compromising biobehavioral consequences of social relationships and their underlying mechanisms.

Attachment and Development

Early Development and Attachment Processes

Attachment refers to the tendency to seek closeness with particular others and to feel more secure in their presence. Initially, attachment processes were conceptualized in both animal and human studies as the need for infant closeness to the mother, although it is now believed that any sensitive, nurturant caregiver can provide these benefits. In early studies with monkeys, Harlow and Harlow (1962) found that close contact with a mother or caregiver is important to normal development. Monkeys raised with an artificial terry cloth mother and isolated from other monkeys during the first 6 months of life show disruptions in their subsequent adult social behavior. They fail to interact normally with other monkeys, their sexual responses are inappropriate, and they show either highly fearful or abnormally aggressive behaviors. They also are less likely to groom other monkeys, and the females that have children become poor mothers, at least with their firstborns.

Similar adversities are found in human offspring who are exposed to long separations from their primary caregivers. In early work with children separated from their mothers, Spitz and Wolf (1946) reported that these children showed high levels of emotional disturbance, especially severe depression. More recent findings regarding Romanian and other Eastern European abandoned infants confirm that without the affectionate attentions of caregivers, the infants fail to thrive, and many die (Carlson & Earls, 1997). Failure to thrive is a complex disorder characterized by a lack of growth and development, and it has both psychological and biological correlates that often can lead to systemwide dysfunction. Failure to thrive has been characterized by a relative imbalance of catabolic (i.e., cortisol, catecholamines) to anabolic (growth hormone, insulin) hormones (Epel, McEwen & Ickovics, 1998; Verdery, 1995). This overabundance of catabolic hormones can lead not only to inhibition of growth hormone but also to malabsorption of nutrients during digestion, thereby further exacerbating growth problems (Sapolsky, 1998). The infants who do survive often have profound deficiencies in both physical growth and mental development, as well as marked dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis, which is vital in biological responses to stress (Carlson & Earls, 1997).

Bowlby (1946), who developed attachment theory, reported that children who experienced early and protracted separations from their caregivers were at risk for a range of emotional and behavioral disturbances. The inability to form a secure attachment to one or more people in the early years, Bowlby argued, interferes with the ability to develop close relationships in adulthood (Bowlby, 1973). Attachment processes in human infants and young children have commonly been studied through a methodology known as the *separation paradigm*. Typically, a mother-infant pair is brought into the laboratory. After an initial period of adjustment to the novel situation, the mother leaves and eventually returns to the experimental room. During the caregiver's absence and again upon return, the infant is observed through a one-way mirror, and his or her activity level, play, crying and signs of distress, and attempts to gain the attention of the mother and willingness to interact with her upon her return are measured. On the basis of these behaviors, infants are categorized into one of three groups. A first group of securely attached infants (about 70%) shows moderate distress at the mother's departure and acknowledges her return. The remaining 30% of infants show one of three insecurely attached patterns. One group of insecurely attached/avoidant babies shows little distress upon the departure of the mother and little enthusiasm upon her return; these infants often ignore her or do not interact with her directly. A second group of insecurely attached/ambivalent infants both seeks and resists physical contact; these infants may cry to be picked up but squirm to get down, and they may cry passively on the mother's departure but fail to

approach her when she returns. The third group of insecurely attached infants shows a disorganized attachment style (Main & Solomon, 1990); these infants appear disoriented, emotionless, and depressed during the separation procedure and, upon the mother's return, approach and then avoid her. Children who fail to thrive are disproportionately more likely to show this disorganized attachment style than normally growing children.

The main determinant of whether an infant develops a secure attachment is whether he or she is in the care of a sensitively responsive caregiver. For example, mothers of securely attached infants usually respond quickly when a baby cries and are affectionate as they pick up the baby. They meet the baby's needs quickly and use the baby's signals to determine when feeding should begin and end, in contrast to the mothers of insecurely attached infants, who typically respond to their own rather than their babies' needs. The mothers of children with the disorganized attachment pattern commonly show little maternal sensitivity (Ward, Kessler, & Altman, 1993). Maternal sensitivity is multidetermined and can be affected by a number of interconnected biological and social variables, including the stressfulness of the present environment, past experiences, and hormone levels (Fleming, O'Day, & Kraemer, 1999).

Attachment and the Development of Stress-Regulatory Systems

Attachment processes are important because they affect both future social relationships and the development of stress-regulatory systems. Specifically, attachment influences how infants and children respond in stressful situations by moderating physiological and neuroendocrine responses to stress. Stressful circumstances produce immediate changes in sympathetic nervous system activity, including elevations in heart rate and blood pressure. Alterations in HPA functioning also occur. Specifically, in response to stress, the hypothalamus releases corticotrophin-releasing hormone (CRH), which stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH), which in turn stimulates the adrenal cortex to release corticosteroids (e.g., cortisol, corticosterone). This integrated pattern of HPA activation is a critical component of the stress response because it modulates a wide range of somatic functions needed for appropriate responses to stress (e.g., energy release, immune activity, mental activity, growth, and reproductive function). Appropriate cortisol regulation (i.e., increased cortisol levels in response to stress followed by decreased cortisol, an indicator of HPA responses to stress) allows the body to respond to stress by preparing for short-term demands. There are costs associated with the stress response as well, and persistent activation of the HPA system (e.g., chronic elevated cortisol levels) may be associated with deleterious effects on the development of physical, cognitive, and emotional functioning (e.g., Gunnar, 1998; Liu et al., 1997; Meaney et al., 1996; Sapolsky, 1996). For example, Meaney and colleagues (e.g., Frances, Diorio, Liu, & Meaney, 1999; Liu et al., 1997; Liu et al., 2000) explicitly link caregiving to infant stress responses and demonstrate consequent effects on the development of stress-regulatory systems. In one of their paradigms, infant rats are removed from the nest, handled by a human experimenter, and then returned to the nest. The immediate response of the mother is intense licking and grooming and arched-back nursing, which provides the pup with nurturant and soothing immediate stimulation; over the long term, this maternal behavior results in better regulation of somatic growth and neural development, especially the enhancement of hippocampal synaptic development and consequent spatial learning and memory.

Early contact with a caregiver and concomitant attachment processes appear to be implicated in physiological and neuroendocrine stress responses in human infants and children, just as they are in animal studies. For example, Gunnar and her associates studied 15-month-old children receiving well-baby examinations and inoculations. Those infants who were securely attached were less likely to show elevated cortisol responses to these normal stressors (i.e., inoculations) than those who were insecurely attached (Gunnar, Brodersen, Kruger, & Rigatuso, 1996; Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996). These protective effects of secure attachment were especially evident for socially fearful or inhibited children. Hart, Gunnar, and Cicchetti (1996) found that children who had been physically abused in their families had disturbances in normal cortisol rhythms (see also Hertsgaard, Gunnar, Erickson, & Nachmias, 1995). Likewise, in a study of 264 infants, children, and adolescents, Flinn and England (1997) found that a family environment characterized by few positive affectionate inter-

actions and a high level of negative interactions, including irrational punishment and unavailable or erratic attention from parents, was associated with abnormal cortisol response profiles, diminished immunity, and frequent illnesses (see also Chorpita & Barlow, 1998).

Separation from the attachment figure has been associated with potentially permanent changes in stress reactivity. For example, extended daily maternal separation of rats during the first 2 weeks of life resulted in elevated ACTH and CRH reactivity to stressors in adulthood (Plotsky & Meaney, 1993), indicating a permanent change in the stress response as a result of early separation experiences. There is some evidence that separation can have long-lasting effects in humans as well. Luecken (1998) found that individuals who had lost a parent during childhood demonstrated altered patterns of stress reactivity as adults, specifically elevated cortisol responses to a laboratory speech task, compared with those who had not lost a parent. Separation from a parent does not uniformly lead to detrimental effects, however. In several studies with monkeys, the magnitude of the stress response when separated from a parent was dependent on the availability of a surrogate parent or another source of social support (Levine, 1993; Reite, Kaemingk, & Boccia, 1989). Gunnar, Larson, Hertsgaard, Harris, and Brodersen (1992) found a similar pattern in human infants: The stress response due to a brief separation period from the mother was virtually eliminated when the infant was left in the care of a responsive, warm, attentive caregiver.

Thus, on the basis of results from both animal and human studies, it appears that a strong and nurturant relationship with a primary caregiver is important for the development of an appropriate biological stress-regulatory system, especially appropriate HPA responses to acutely stressful circumstances. Importantly, however, the availability of an alternative attachment figure can buffer the stress response to separation from the primary attachment caregiver.

Social Support and Biobehavioral Responses to Stress

Adult Social Support

A growing literature indicates that social support processes buffer sympathetic and HPA responses to acute stress in adults as well. In a typical investigation, an individual is brought into the laboratory either alone, with a friend, or with a supportive stranger; asked to go through stressful tasks (such as mental arithmetic or giving a speech in front of an audience); and assessed as to sympathetic and neuroendocrine functioning initially, at peak stress, and again during a recovery period. The presence of a supportive person, whether friend or stranger, consistently has been shown to reduce sympathetic (SNS) and HPA responses to stress and facilitate recovery from the physiological effects of acute stress (e.g., Fontana, Diegnan, Villeneuve, & Lepore, 1999; Glynn, Christenfeld, & Gerin, 1999; Kirschbaum, Klauer, Filipp, & Hellhammer, 1995; Seeman and McEwen, 1996, for a review).

These findings are potentially of great importance in accounting for the beneficial health effects of social support. Chronic exposure to stressful environments taxes and may ultimately alter sympathetic activity in response to stress, laying the groundwork for chronic disorders such as coronary heart disease (CHD) and cardiovascular disease (Uchino, Cacioppo, & Kiecolt-Glaser, 1996). Allen, Matthews, and Sherman (1997), for example, found that cardiovascular reactivity to stress among boys as young as 8 to 10 years old was associated with increased left ventricular mass, a risk factor for CHD. Ballard, Cummings, and Larkin (1993) found that children of hypertensive parents showed heightened systolic blood pressure reactivity to angry exchanges between adults, responses that may be precursors of later difficulties in stress management and risk for hypertension. The adverse effects of stress on SNS and HPA functioning, in turn, may adversely affect immune functioning (Uchino, Uno, & Holt-Lunstad, 1999). Immune functioning is related both to infectious disease and to more chronic, life-threatening diseases such as cancer and HIV infection progression. For example, Cohen, Doyle, Skoner, Rabin, and Gwaltney (1997) found that individuals with more diverse social networks were less likely to develop respiratory infections following experimental exposure to a virus than were those persons with less diverse networks.

Sympathetic reactivity in response to stress also may reflect contributions from the parasympathetic nervous system. Like sympathetic activity, parasympathetic activity is responsive to cognitive and emotional states, and chronic negative emotions, such as anxiety and hostil-

ity, have been associated with lower heart rate variability, a marker of reduced parasympathetic response (Kawachi, Sparrow, Vokonas, & Weiss, 1994; Sloan et al., 1994). Lower heart rate variability, in turn, has been linked to increased health risks (Kristal-Boneh, Raifel, Froom, & Rivak, 1995). These findings suggest that chronic stress, unmitigated by social support, may lead to reductions in parasympathetic activity, which is an important counterregulatory break on sympathetic activity. Any such reductions would contribute to the greater overactivation of the sympathetic response to stress and lead to a propensity for chronic disorders, such as hypertension and CHD.

Chronic HPA activation can lead to permanent alterations in HPA reactivity, with potential long-term implications for immune-related disorders, as well as for cognitive and emotional functioning. In particular, persistent activation of the HPA system is associated with immune deficiencies, inhibited growth, delayed sexual maturity, damage to the hippocampus, cognitive impairment, and psychological problems such as depression (Sapolsky, 1998; Seeman & McEwen, 1996).

Whether the beneficial health effects of social support can be largely accounted for by the regulation of the sympathetic and HPA responses to stress is unknown at present. It seems likely, though, that such processes account for some of the observed beneficial health effects of social support (Cacioppo & Berntson, 1992; Uchino et al., 1999). The question we next address is whether there is evidence for other biological regulatory mechanisms being implicated in the processes by which social support yields beneficial health effects. For example, in addition to reducing the adverse effects of stress on biological regulatory systems, might social support restore, result in, or actively foster a physiological and neuroendocrine environment that is conducive to good health? In our discussion, we will focus specifically on the involvement of oxytocin and endogenous opioid peptides and their possible role in muting adverse physiological and neuroendocrine responses to stress.

Oxytocin, Social Support, and Responses to Stress

Oxytocin is a peptide released from the posterior pituitary in response to stress and touch and during breastfeeding. Oxytocin has been heavily studied concerning its role in milk ejection during nursing and uterine contractions during labor, but only recently have its potential roles in the neurobiology of stress responses and in affiliative responses to stress been examined (Taylor et al., 2000). Several lines of evidence from animal and human studies suggest a potential role for oxytocin in the beneficial effects of social support on health: Oxytocin is implicated in the development of attachment relationships; oxytocin is secreted in response to stress; oxytocin stimulates pro-social contact; social contact leads to the secretion of oxytocin (at least in some species); and oxytocin is associated with down-regulation of sympathetic and HPA responses, with concomitant anxiety reduction.

Oxytocin is one of the earliest hormones to be released in response to at least some sources of stress (Sapolsky, 1996), and based on evidence from animal studies, it may be implicated in the down-regulation of sympathetic and HPA responses to stress. McCarthy (1995) maintains that, among animals in the natural environment that face a constant barrage of stress, oxytocin is associated with parasympathetic functioning, which, as just noted, plays a counterregulatory role in fear responses to stress (Dreiffus, Dubois-Dauphin, Widmer, & Raggenbass, 1992; Sawchenko & Swanson, 1982). In experimental studies with animals, oxytocin enhances sedation and relaxation, reduces behavioral indications of anxiety, and decreases sympathetic activity (Altemus et al., 1997). Exogenous administration of oxytocin in rats results in decreases in blood pressure, pain sensitivity, and corticosteroid levels, among other findings indicative of a reduced stress response (Uvnas-Moberg, 1997). Oxytocin also appears to inhibit the secretion of ACTH and cortisol in humans (Chiodera & Legros, 1981; Legros, Chiodera, & Demy-Ponsart, 1982).

Human studies also are suggestive as to a role for oxytocin in down-regulating responses to stress. Taylor, Klein, Greendale, and Seeman (2000) found that oxytocin release in response to stress was associated with reduced cortisol responses during stress and a more rapid return to baseline during recovery. Lower levels of sympathetic arousal and HPA responses to stress have been found in lactating versus nonlactating women (Adler, Cook, Davidson, West, & Bancroft, 1986; Altemus, Deuster, Galliven, Carter, & Gold, 1995; Wiesenfeld, Malatesta, Whitman, Grannose, & Vile, 1985). Thus, oxytocin may have beneficial effects on animals

and humans, especially in stressful circumstances, by muting sympathetic and HPA responses to stress.

A growing literature also suggests that there are affiliative concomitants of oxytocin, thereby implicating this hormone in support seeking in response to stress. Studies of ewes have found that central nervous system (intracerebroventricular) administration of oxytocin stimulates maternal behavior (Kendrick, Keverne, & Baldwin, 1987). The resulting grooming and touching that occurs in mother-infant contact may help soothe infants under stressful conditions. These effects appear to be bidirectional inasmuch as oxytocin enhances affiliative and affectionate contact with offspring, which in turn enhances the flow of oxytocin. In studies with rats, administration of an oxytocin-blocking agent diminished the attractive qualities of conditioned maternal cues (Panksepp, Nelson, & Bekkedal, 1999). Social contact is enhanced and aggression is diminished following central oxytocin treatment in estrogen-treated prairie voles (Witt, Carter, & Walton, 1990), and in experimental studies with female rats, the administration of oxytocin causes an increase in social contact and in grooming (Argiolas & Gessa, 1991; Carter, DeVries, & Getz, 1995; Witt, Winslow, & Insel, 1992). Because social contact is protective against certain forms of stress (such as attack by predators), and because such protection may be especially helpful to females nurturing infants, oxytocin-facilitated affiliative responses to stress are thought to represent an adaptive response to stressful circumstances (Drago, Pederson, Caldwell, & Prange, 1986; Fahrbach, Morrell, & Pfaff, 1985; McCarthy, 1995). In summary, oxytocin, released in response to stress, appears to induce a state of mild sedation and relaxation, reduce anxiety, decrease sympathetic and HPA activity, and promote affiliative and pro-social behavior under stressful circumstances.

Oxytocin also may be implicated in many forms of human social attachment, including caregiver-infant attachments, adult pair bonds, and other forms of affiliative behavior such as friendship (Carter, 1998; Carter & Altemus, 1997). For example, Uvnas-Moberg (1996) found that women who were breastfeeding and, therefore, had very high levels of plasma oxytocin, perceived themselves as feeling calmer and rated themselves as more social than did age-matched women who were not breastfeeding or pregnant (i.e., who had lower amounts of plasma oxytocin). Moreover, the level of plasma oxytocin in these breastfeeding women correlated strongly with the level of calm reported and oxytocin pulsatility (changes in oxytocin) was significantly correlated with self-reported sociability (Uvnas-Moberg, 1996). Oxytocin may be related either to enhanced perceptions of one's sociability and the positivity of one's social relationships or to behavioral tendencies that lead to more pro-social activity or both. Dunn and Richards (1977) reported higher levels of maternal behavior among lactating versus nonlactating new mothers. Keverne, Nevison, and Martel (1999) suggested that other bonding relationships may have piggybacked onto the evolutionary adaptation of maternal-infant bonding and the corresponding attachment processes. Consistent with this hypothesis, animals prefer to spend time with animals in whose presence they have experienced high brain oxytocin in the past, suggesting that friendships may be mediated at least in part by the same system that mediates maternal urges.

As is true for rats and primates, human responses to stress are often characterized by affiliation (see Taylor et al., 2000). The conclusion from reviews of the literature is that affiliative responses to stress may be more characteristic of women than men. The high investment of girls and women in the creation and maintenance of social networks, relative to boys and men, is one of the most robust gender differences in adult human behavior, and it is the primary gender difference in adult human behavioral responses to stress (Belle, 1987; Luckow, Reifman, & McIntosh, 1998). Across the entire life cycle, females are more likely to mobilize social support in times of stress, especially from other females. They seek it out more, they receive more support, and they are more satisfied with the support they receive (Belle, 1987; Copeland & Hess, 1995; McDonald & Korabik, 1991; Ogus, Greenglass, & Burke, 1990; Ptacek, Smith, & Zanas, 1992; Wethington, McLeod, & Kessler, 1997).

In the early studies on affiliation under conditions of stress, the primary focus was on females because the affiliative response to stress was reliable only in female participants (Schachter, 1959). A survey study (Veroff, Kulka, & Douvan, 1981) found that women were 30% more likely than men to have provided some type of support in response to network stressors. In their analysis of gender differences in coping, Luckow et al. (1998) found that the larg-

est difference arose on "seeking and using social support," and the combined statistical significance of this effect was significant beyond the $p < .0000001$ level. Specifically, of the 26 studies that tested for gender differences, 1 study found no differences, and 25 studies favored women's greater seeking and use of social support; there were no reversals. Moreover, these findings have substantial cross-cultural generalizability. In a study of 6 cultures, Whiting and Whiting (1975) found that women and girls sought more help and gave more help to others than did men in stressful times, and Edwards (1993) found similar sex differences across 12 additional cultures.

Oxytocin may be at the core of these sex differences in affiliation, in that the effects of oxytocin may be more pronounced in females than in males. Animal studies show that (a) oxytocin release in response to stress appears to be greater in females than in males (Jezova, Jurankova, Mosnarova, Kriska, & Skultetyova, 1996); (b) there appears to be an inhibitory action of androgen on oxytocin release under conditions of stress, thereby potentially limiting its effects on males during stressful conditions (Jezova et al., 1996); and (c) the effects of oxytocin appear to be strongly modulated by estrogen such that estrogen enhances the anxiolytic (antianxiety) properties of oxytocin (McCarthy, 1995; Windle, Shanks, Lightman, & Ingram, 1997). Taylor and her associates (Taylor et al., 2000) found oxytocin release in response to stress to be greater in postmenopausal women who were on estrogen replacement therapy than in those who were not, suggesting a facilitating effect of estrogen on oxytocin in humans as well.

To summarize, oxytocin is secreted by mothers in many species immediately following the birth of offspring, and it may facilitate the behaviors that lead to the attachment processes typically seen between mother and offspring. Oxytocin is released in response to (at least some) stressors in both animals and humans; moreover, it is associated with reduced sympathetic and HPA responses, and with increases in pro-social behaviors under stress (e.g., as seeking the company of others in both animal and human studies). The particular tendency for women to seek and provide social support under stress, coupled with animal data suggesting that the concomitants of oxytocin may be true primarily for females (down-regulation of stress responses, increase in maternal and other affiliative behaviors), leads to potentially important inferences: Oxytocin may have a general role in underlying human affiliative responses to stress and a particular role for social responses to stress in women (Taylor et al., 2000).

How might oxytocin play a role in the health benefits of social support? Many illnesses including acute disorders such as colds and flus as well as CHD, are thought to result from stress-related wear and tear on stress-regulatory systems, including the SNS and HPA responses just described. If oxytocin release in response to social contact mutes these responses, then it may reduce the wear and tear on these systems thereby limiting vulnerability to disease initially and/or facilitating the likelihood of recovery. Other mechanisms also may be implicated in the beneficial effects of social support, however, and we now turn our attention to those.

Opioid Mechanisms, Social Support, and Stress

Based on evidence from animal studies, endogenous opioids also may be implicated in the beneficial effects of social relationships on health. As is true of oxytocin, the secretion of endogenous opioid peptides appears to occur in response to positive social contact, and as is also true for oxytocin, endogenous opioid secretion has been tied to down-regulation of sympathetic and HPA responses to stress.

Much of the work relating endogenous opioids to affiliative behavior has been conducted with animals in studies by Panksepp and associates (e.g., Nelson & Panksepp, 1998; Panksepp, 1998). These researchers' brain opioid theory of social attachment has several supportive lines of investigation, including the following points: (a) endogenous opioids are released during social contact; (b) endogenous opioid peptide release attenuates distress in response to social separation; (c) endogenous opioids are rewarding and can produce odor and place preferences; and (d) low levels of endogenous opioids can act as an incentive to seek social contact (Nelson & Panksepp, 1998).

As is true for oxytocin, endogenous opioid mechanisms are implicated in maternal attachment processes in animals. In a study with rhesus monkeys, administration of an endogenous opioid peptide-blocking agent, naloxone, was associated with less caregiving and protective behavior toward infants (Martel, Nevison, Rayment, Simpson, & Keverne, 1993). Similarly,

administration of naltrexone, also an opioid antagonist, inhibits maternal behavior in sheep under experimental conditions (Kendrick & Keverne, 1989). In studies with rats, administration of opioid antagonists blocked behavioral indicators of infant-mother attachment (Panksepp, Nelson, & Bekkedal, 1999). As one would expect, then, the mother-infant separation paradigm, coupled with experimental manipulation of opioid agonists and antagonists, has been useful for examining the impact of endogenous opioids on distress indicators. Separation reliably produces behavioral indications of anxiety and distress vocalizations. Consistent with Panksepp's model, administration of opioid agonists reliably leads to reductions in distress vocalizations in a broad array of species; moreover, there is parallel evidence that opioid antagonists enhance such vocalizations (see Nelson & Panksepp, 1998, for a review).

Endogenous opioids also may modulate biological responses to stress. The opioid antagonist naloxone can increase basal levels of ACTH and cortisol, as well as alter stress reactivity (McCubbin, 1993). In a series of experiments, McCubbin and colleagues found that blocking opioid activity with an antagonist increases SNS and HPA responses to stress both in the laboratory (McCubbin, 1993) and in natural settings (McCubbin et al., 1998). Interestingly, they find that those people who demonstrated an elevated SNS response to stress under normal conditions do not show this increase in the stress response with opioid blockade. These findings may have implications for a mechanism of how opioids could reduce stress responses. People who respond to acute stress with high levels of sympathetic activity also have larger stress-related increases in HPA activity and larger changes in immune functioning (Sgoutas-Emch et al., 1994). Additionally, those who respond to acute stress with large increases in SNS activity are not affected by an opioid blockade; that is, they do not appear to have opioid-mediated inhibition of the stress response. Opioid mechanisms have been hypothesized to operate on CRF neurons in the hypothalamus (McCubbin et al., 1998), and CRH can then orchestrate the activation of the HPA and SNS systems. Thus, people with low levels of opioids could have a larger stress response due to larger increases in CRF that would ultimately lead to increases or changes in SNS, HPA, and immune activity. Opioids can also directly regulate heart rate and blood pressure (Verrier & Carr, 1991) and modulate certain aspects of immunity. Over time this constant overactivation due to a faulty opioidergic mechanism could lead to chronic elevations in stress hormones, which, in turn, could increase vulnerability to a variety of health problems and diseases.

Endogenous opioids also may modulate affiliative and social responses to stress. The present evidence for this role of the peptides is clearer for females than for males. In both animal and human studies, higher levels of endogenous opioids are associated with higher levels of social interaction. For example, Martel and associates (1993) found that administration of naloxone in rhesus monkeys reduced females' social grooming of other females. In a study of college women, Jamner, Alberts, Leigh, and Klein (1998) found that administration of naltrexone increased the amount of time that women spent alone, reduced the amount of time they spent with their friends, and reduced the reported pleasantness of the women's social interactions, as compared with those of men. In addition, women given naltrexone rather than a placebo substance initiated fewer social interactions. Parallel effects were not obtained within men. Thus, endogenous opioids may play a role in regulating social interactions, especially for women. Inasmuch as the affiliative response to stress has been reliably documented only in women, these parallel sex differences in the affiliative concomitants of endogenous opioids are intriguing.

As is true of oxytocin, physical contact leads to central endogenous opioid release in a number of species, and such release has been observed in response to rough-and-tumble play, grooming, and holding. Correspondingly, social isolation has been associated with reduced basal endogenous opioid levels, and social contact restores opioid levels and produces a consequent state of euphoria. Through this action, Panksepp (1998; Nelson and Panksepp, 1998) suggests, a social addiction process may result, whereby the release of opioids in response to social stimuli leads to further seeking out of social stimuli. Support for this model, however, remains preliminary, and it is unclear whether it applies to humans.

To summarize the argument thus far, social support has reliable and beneficial effects on health that may be mediated in part or entirely by the down-regulation of sympathetic and HPA responses to stress. Yet the biological mechanisms underlying these effects have been

largely unknown. Both oxytocin and endogenous opioid peptides are released in response to stress and have behavioral (pro-social) and biological (down-regulation of stress responses) consequences that may be implicated in these mechanisms. To date, however, the evidence for the role of these hormones in the propensity to seek and provide social support, as well as their role in down-regulating stress responses, is more plentiful for women than for men.

Additional Potential Biological Substrates of Human Social Behavior

The animal literature on affiliative responses to stress reveals other tantalizing clues for exploration in humans. Vasopressin, a posterior pituitary hormone that is similar in structure to oxytocin, may have a role in affiliation in young rats, especially contact with the mother. In the prairie vole, vasopressin is linked to paternal behavior and to males' guarding of mothers and infants during times of stress. Vasopressin may be implicated in male-female pair bonds at least in some species, and there is a modest literature linking vasopressin to memory for social stimuli (Englemann, Wotjak, Neumann, Ludwig, & Landgraf, 1996). The role that vasopressin may play in human affiliative responses, especially those exhibited under stress, as yet is unknown. Based on intriguing evidence from animal studies, vasopressin may play a particular role in males' social responses.

Norepinephrine, serotonin, and prolactin also may be involved in social responses to stress, although they have received less attention. Specifically, norepinephrine, a catecholamine also released during stress, has been implicated in olfactory learning related to social stimuli and to maternal behavior in animals (Nelson & Panksepp, 1998). In particular, norepinephrine projections to the olfactory bulb are believed to underlie maternal learning in some species, enabling mothers to identify and approach their own young. Norepinephrine also may be involved in social affect and social memory in primates (e.g., Kraemer, 1992). The role of norepinephrine in social behavior in humans is presently unknown. Serotonin also may be involved in animal and human social relationships. Alterations in serotonergic functioning are implicated in the frequency of rat pup separation distress calls, and serotonergic enhancers have been related to affiliative gestures, increased grooming, and a rise in the dominance hierarchy in some old-world monkey species (Insel & Winslow, 1998). In humans, serotonin is associated with social confidence and feelings of connectedness to others, and reduction in brain serotonin activity is a consequence of prolonged social isolation (Nelson & Panksepp, 1998). Prolactin also may be an important stress-related hormone. For example, increases in prolactin levels have been observed in bereaved women, and these levels correlated with grief and depression scores (Lane et al., 1987).

Conclusions

In summary, there is evidence that oxytocin, endogenous opioids, and perhaps vasopressin, norepinephrine, and serotonin may play significant roles in affiliation in a variety of mammalian species and potentially in humans as well. Indeed, Panksepp and associates (e.g., Nelson and Panksepp, 1998; Panksepp, 1999) have argued that they are part of a unitary brain process of affiliative circuitry that regulates mammalian affiliative behavior. First activated in the context of maternal-infant bonding (or, in the case of humans, caregiver-infant bonding), this system that results in attachment appears to underlie both biological responses to stress and the development of the biological stress-regulatory systems themselves. This system also may underlie a broad array of social relationships across the life span, as well as their beneficial effects on health; exactly how this works is unknown at present. In addition, the extent to which hormonal regulation is critical for extrafamilial relationships or adult relationships, especially in humans, remains unknown. The presence of a large neocortex, which facilitates the acquisition and learning of information, means that much human social behavior is freed from exclusive hormonal control, but whether there still may be some aspects of hormonal initiation or control of social behavior under stress is as yet unknown.

In the literature to date, it appears that there may be differences between men and women in the neuroendocrine underpinnings of seeking social support and in the neuroregulation of the benefits of social support as well. These divergences are somewhat surprising, inasmuch as both men and women show health benefits of social support. The pathways appear to be somewhat better charted in women than in men. Specifically, in females, oxytocin and endoge-

nous opioid peptides are released in response to (at least some) stressors, prompting affiliative responses and leading to down-regulation of sympathetic and HPA responses to stress. In addition, both sexes also may profit from the appraisal benefits that appear to come from the availability of social support on sympathetic and HPA concomitants of stress, the routes by which the health benefits of social support have customarily been thought to occur (Seeman & McEwen, 1996; Uchino et al., 1996). Exactly how and if vasopressin, serotonin, and prolactin may be involved in these processes is unknown. The fact that social support has such clear health benefits, however, underscores both the likelihood and the importance of the role that biological mechanisms play in affiliative processes, including affiliation under stress.

Though long acknowledged, the psychologically and biologically protective aspects of social support are only beginning to be understood. Despite gaps in the evidence, it is clear that human beings' social relationships can contribute substantially to optimum functioning, constituting a significant resource. Such findings underscore a broader point, namely, that as researchers increasingly uncover the dimensions of the positive psychology of optimum functioning, charting the interplay of biology and behavior and the biobehavioral pathways by which such strengths exert protective effects on mental and physical health will be vital to this effort.

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