Interaction among Social Environment, 
the Hypothalamic–Pituitary–Adrenal 
Axis, and Behavior

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INTRODUCTION

“The most basic questions in the field do not deal narrowly with effect of hormones on organisms, but with the ways in which hormones influence interactions between organisms and their environments.”

Frank A. Beach (1985)

The term “stress” was borrowed from the fields of physics and engineering to describe the biological state of disrupted homeostasis (Selye, 1950). Since then, the concept of stress has become ingrained in the scientific literature and popular press; yet, no consensus has been achieved for a precise definition of biological stress (McEwen, 2000). Often, increased concentrations of hypothalamic–pituitary–adrenal (HPA) axis hormones, particularly corticosterone (CORT) or cortisol, are used as an index of stress and any stimulus that causes an increase in HPA axis activity is identified as a stressor. Because most stressors tend to be noxious stimuli, the state of stress has acquired a negative connotation. Indeed, formal studies of stress, particularly biomedical studies, have focused primarily on the pathological or maladaptive consequences of stress or activation of the HPA axis. In many cases, however, the so-called stress responses are initially adaptive responses that enable organisms to respond to environmental change. The pathological consequences of stress occur only after prolonged exposure to the stressor or mediators of the stress response, including hormones of the HPA axis (reviewed in Sapolsky, 1992). Several recent studies have documented that activation of the HPA axis can have adaptive consequences that may or may not be coupled to responses to stressors. For example, social and situational factors can alter HPA axis function to influence partner attraction or preference formation in some species. Altered HPA activity also can influence social organization (i.e., promotes/inhibits monogamy) on a proximate basis (DeVries, DeVries, Taymans, and Carter, 1996, 1995).

In this paper, I will describe how the HPA axis plays a role in normal social preference and pair-bond formation. Using an animal model of cerebrovascular damage, I also will illustrate how exposure to positive versus negative social factors can alter HPA axis activity and subsequently affect disease outcome. Finally, I will discuss the role of oxytocin as one mechanism through which positive social cues may suppress the HPA axis.

PRAIRIE VOLE HPA AXIS AND RESPONSE TO SOCIAL STIMULI

Prairie voles (Microtus ochrogaster) exhibit atypical regulation of the HPA axis. Serum CORT concentrations are approximately 10 fold higher in these arvicoline rodents than in rats (Rattus norvegicus); Prairie voles exhibit threefold increase in circulating ACTH concentrations and increased adrenal-to-body weight ratios (Taymans, DeVries, DeVries, Nelson, Friedman, Castro, Detera-Wadleigh, Carter, and Chrousos, 1997). High corticosteroid binding globulin (CBG) concentrations in prairie vole blood partially compensate for the excess CORT in this species (Taymans et al., 1997). CORT that is bound to CBG is prevented from entering cells and crossing the blood-brain barrier (Siiteri,
Murai, Hammond, Nisker, Raymoure, and Kuhn, 1982). Despite increased CBG concentrations in prairie voles, concentrations of “unbound” or “free” CORT are still significantly higher in prairie voles than rats. The potentially negative impact of the chronic high free corticosteroid concentrations is also reduced by a decrease in glucocorticoid (Type II) receptor affinity and density in central and peripheral tissue of prairie voles compared to rats (Hastings, Orchinik, Aubourg, and McEwen, 1999; Taymans et al., 1997). The reduced prairie vole glucocorticoid receptor affinity may be due to several nonconserved amino acid substitutions that occur in the steroid-binding domain of the receptor gene (Taymans, 1996). Despite the extraordinarily high serum concentrations of CORT, the hypothalamic–pituitary–adrenal (HPA) axis in prairie voles is responsive to circadian cues and stressors (DeVries et al., 1996; Taymans et al., 1997). However, it is resistant to dexamethasone-induced suppression (Taymans et al., 1997). Dexamethasone is a synthetic, high affinity, glucocorticoid that has been used in several species to assess negative feedback sensitivity of the HPA axis. Resistance to dexamethasone suppression suggests impaired glucocorticoid-mediated negative feedback regulation of the HPA axis (Taymans et al., 1997). Taken together, these unusual physiological characteristics of prairie voles suggest that they may be a glucocorticoid-resistant species (Hastings et al., 1999; Taymans et al., 1997). Glucocorticoid resistance is often considered a pathological condition in humans (Chrousos, Vingerhoeds, Brandon, Eil, Pugeat, DeVroede, Loriaux, and Lipsett, 1982b). Glucocorticoid resistance is also observed in guinea pigs and some species of New World primates, but it has been argued that glucocorticoid resistance in nonhumans may be a nonpathological, potentially adaptive, response to unidentified selective pressures (Chrousos, Renquist, Brandon, Eil, Pugeat, Vigersky, Cutler, Loriaux, and Lipsett, 1982a).

Although prairie voles appear to be relatively insensitive to pharmacological suppression of the HPA axis, they are exceptionally sensitive to suppression by social cues (DeVries, Taymans, and Carter, 1997b; DeVries et al., 1995). For example, exposing socially naive prairie voles to a novel animal of the opposite sex reduces serum CORT concentrations within 15 minutes of pairing in males and 60 minutes of pairing in females (DeVries et al., 1997b, 1995). Corticosteroids remain suppressed in both sexes for more than three hours after pairing. The mechanism through which CORT declines following introduction of a novel animal is not known, but the effect appears to be dependent on the social history of the experimental animals and the sex of the stimulus animals. When pair bonded females are exposed to a novel male, corticosteroid concentrations tend to increase rather than decrease (DeVries et al., 1995). In contrast, male prairie voles, regardless of social history, exhibit a significant decline in CORT concentrations following pairing with a novel female (DeVries et al., 1997b). When the experimental and stimulus animals are the same sex, however, there is no change in serum CORT concentrations following pairing (DeVries et al., 1997b, 1995). The unusual response pattern and heightened sensitivity of the HPA axis to specific social cues in this monogamous species suggests that corticosteroids may be an important mediator of social bonding (see Table 1).

### HPA AXIS AND MONOGAMY

Field and laboratory studies indicate that prairie voles form long-term pair bonds and are socially monogamous (Carter, DeVries, and Getz, 1995). Monogamy is relatively rare among mammals (Kleiman, 1977), but in prairie voles it is associated with several selective advantages including increased pup survival (Getz, Larson, and Lindstrom, 1992), accelerate pup development (Wang and Novak, 1992), and social buffering against stress (Carter, 1998). The ultimate factors underlying monogamy have been well-consid-
ered, but until recently, little was known regarding the proximate regulation of monogamy. Typically when socially naive prairie voles meet, they engage in a brief period of olfactory investigation, followed by prolonged periods of close physical contact (Getz, Carter, and Gavish, 1981). Behavioral estrus in these females does not occur for approximately 24–48 h after contact with a novel male (Carter, 1998). If the male and female prairie voles remain in close contact, it is likely that a social bond would form prior to the onset of behavioral estrus and mating (DeVries and Carter, 1999; DeVries, Johnson, and Carter, 1997a). Therefore, we set out to determine the functional significance of the decline in CORT observed following pairing of socially naive female and male prairie voles.

In the laboratory, preference for social contact with a familiar partner is used as an index of pair bonding. Following cohabitation of the experimental animal and its new partner, social preferences are assessed using a three-chamber apparatus that allows the experimental animal to choose among spending time alone, with the familiar partner, or with the novel stimulus animal (stranger). The amount of time spent in physical contact with the partner and stranger is recorded during the three-hour preference test. A social preference is assigned when the experimental animals spend significantly more time in physical contact with one stimulus animal than the other. Using this behavioral paradigm, females that are adrenalectomized to artificially lower blood CORT concentrations form social preferences after shorter cohabitation periods than sham-operated animals (DeVries et al., 1995). In contrast, exposure to stress or treatment with exogenous CORT prior to cohabitation with the partner results in a social preference for the novel male (DeVries et al., 1996, 1995). These partner preference data support the hypothesis that naturally occurring fluctuations in CORT concentrations alter the development of social bonds in female prairie voles (DeVries et al., 1995). Low circulating CORT concentrations in socially naive females appear to facilitate the formation of a partner preference, whereas the increase in CORT concentrations that occurs in paired females under comparable conditions may act to preserve an existing social bond by preventing the female from forming a preference for the novel male.

The behavioral processes associated with the formation and expression of social preferences in male and female prairie voles appear to be superficially similar (DeVries and Carter, 1999; DeVries et al., 1997a). However, the effect of stress on pair bond formation is sexually dimorphic. In contrast to females, exposure to a moderate stressor or treatment with exogenous CORT facilitates the induction of partner preferences in male prairie voles (DeVries et al., 1996). When endogenous CORT concentrations are reduced in male prairie voles via adrenalectomy, the normal formation of partner preferences is blocked and the males tend to prefer a novel female (DeVries et al., 1996). Intracerebroventricular doses of corticotropin-releasing factor (CRF; 0.1 and 1.0 ng) also facilitate the formation of social preferences in male prairie voles (DeVries, Guptaa, Cardillo, Cho, and Carter, 2002). However, at doses 10–100 times higher than those effective in producing partner preferences, CRF has deleterious effects on social bonding, which most likely is due to increased anxiety associated with excess CRF (Shultz et al., 1996). Thus, in male prairie voles, low circulating CORT concentrations inhibit the formation of a partner preference, whereas exposure to stress or an increase in stress-related hormones facilitates social bonding. Unlike female prairie voles, males do not form partner preferences during the first several hours of social interaction while CORT concentrations are low. Unmanipulated male prairie voles require approximately 24 h of cohabitation to exhibit a social preference (DeVries and Carter, 1999), by which time corticosteroid concentrations are returning to baseline values.

Taken together, these studies provide evidence that social stimuli can alter HPA axis activity, and that HPA axis activity, in turn, is capable of influencing the formation of adult social preferences, the first necessary step in the formation of social bonds. Involvement of the HPA axis in pair bond formation also provides a mechanism through which environmental challenges can influence social structure in prairie vole populations. Although it has been demonstrated that environmental factors such as short day lengths and low temperatures increase basal corticosteroid concentrations in prairie voles (Nelson, Asfaw, DeVries, and Demas, 1996), the effects of adverse environmental conditions on pair bonding remains to be specified (cf., Cushing, Martin, Young, and Carter, 2001).

The formation of social preferences between male and female prairie voles also can be facilitated by mating (Williams, Insel, Harbaugh, and Carter, 1994; Winslow, Hastings, Carter, Harbaugh, and Insel, 1993) or treatment with mating-related hormones such as vasopressin (AVP) or oxytocin (OT; Cho, DeVries, Williams, and Carter, 1999; Cushing and Carter, 2000; Insel and Hulihan, 1995; Williams et al., 1994) (see Table 2). More recently, a role for dopamine (DA) in pair bonding has been proposed (Gingrich, Liu, Cascio, Wang, and Insel, 2000; Wang, Yu, Cascio, Liu, Gingrich, and Insel, 1999). Treatment with a dopamine
D-2 receptor antagonist prevents mating-induced partner preference formation (Gingrich, Liu, Cascio, Wang, and Insel, 2000; Wang, Yu, Cascio, Liu, Gingrich, and Insel, 1999) whereas treatment with a D-2 receptor agonist facilitates the formation of partner preferences in female prairie voles (Wang, Yu, Cascio, Liu, Gingrich, and Insel, 1999). Whether the oxytocin, vasopressin, dopamine, and CORT act through a common pathway or distinct pathways to induce partner preferences in prairie voles and other socially monogamous species remains to be determined. However, Young and colleagues have proposed that DA may interact with AVP and OT to facilitate social bonding by sensitizing the mesolimbic dopamine reward system during mating, which ultimately could lead to prairie voles to form a conditioned social preference for their mate (Young, Lim, Gingrich, and Insel, 2001). This hypothesis is based on previously described OT, AVP, and DA partner preference data and the observation that prairie voles have unusually high densities of OT and AVP receptors in some brain regions associated with the mesolimbic dopamine reward system during mating (Young et al., 2001). CORT also may interact with AVP and DA to facilitate partner preference in male prairie voles. AVP is a potent ACTH secretagogue (Gillies, Linton, and Lowry, 1982) which can lead to increased blood CORT concentrations. Furthermore, rats that are stressed or treated with exogenous CORT exhibit increased extracellular DA concentrations in the nucleus accumbens (Rouge-Pont, Deroche, Le Moal, and Piazza, 1998). If the dopaminergic response to stress is similar in prairie voles and rats, then AVP and stress may facilitate partner preference indirectly via corticosteroid effects on DA transmission. Additional research is needed to determine exact nature of interactions among AVP, OT, DA, and CORT in facilitating partner preference.

A role for the HPA axis in social bonding has been investigated in species other than prairie voles, however, most of these studies focus on mother–infant bonds. For example, in sheep, treatment with CRF facilitates maternal acceptance of an orphan lamb (Keverne and Kendrick, 1991) Similarly, first time human mothers with high cortisol concentrations are more attracted to their infant’s odor cues and more affectionate toward their infant than women with relatively low cortisol concentrations (Fleming, Ruble, Krieger, and Wong, 1997a; Fleming, Steiner, and Corter, 1997b). No association between cortisol and maternal attitudes or behavior has been identified in multiparous women (Fleming et al., 1997a). In contrast to humans, urinary cortisol concentration is negatively correlated with the amount of time captive, multiparous, female gorillas spend carrying and supporting their infants (Bahr, Pryce, Dobeli, and Martin, 1998). The apparent discrepancy in relationship between cortisol and maternal behavior in humans and gorillas may represent species differences in hormonal influences on behavior. Alternatively, the relative level of stress experienced by the human and gorilla mothers during the course of the studies described above may have been different. For example, two of the three gorillas with the highest post-partum stress indices and lowest maternal care scores were consistently harassed or attacked by group members (Bahr et al., 1998). Thus, social stress may have increased cortisol concentrations in these animals beyond the level that permits or facilitates optimal expression of maternal behavior.

### ENDOCRINE RESPONSE TO DISRUPTION OF SOCIAL BONDS

Once a social bond has formed, forced disruption of the bond can have several behavioral and physiological consequences. Again, much of the research on this topic involves mother–infant separation (Carter, 1998; Gunnar, 2000), however, separation-induced stress re-
Responses also have been reported in adults of several mammalian species (Table 3). Increased serum cortisol concentration is a commonly used index of separation stress in primates. Adult Titi monkeys (*Callicebus moloch*; Mendoza and Mason, 1986), common marmosets (*Callithrix jacchus*; Norcross and Newman, 1999), and cotton top tamarins (*Saguinus oedipus*; Ziegler, Scheffler, and Snowdon, 1995) exhibit increased blood cortisol concentrations in response to separation from a mate or established partner. Siberian dwarf hamsters (*Phodopus sungorus*) also respond to pair separation with increased HPA axis activity and food intake (Castro and Matt, 1997b) as well as decreased social interactions and exploratory behaviors (Crawley, 1984). Some of these separation-induced behavioral effects are attenuated by treatment with antidepressants (Crawley, 1984). In common with prairie voles, pairing female squirrel monkeys is associated with a decline in cortisol, while disruption of isosexual social bonds causes an increase in cortisol (Mendoza, Hennessy, and Lyons, 1992; Saltzman, Mendoza, and Mason, 1991).

### SOCIAL INTERACTIONS BLUNT HPA AXIS ACTIVATION

It is well documented that stressful or noxious social interactions impair immune function and disease outcome. A large clinical and experimental literature suggests that positive social interactions also have a profound effect on health (Cohen, 1988). Only within the past several years have researchers begun examining the physiological mechanisms underlying the protective effects of social interactions (Cohen, 1988; Uchino, Cacioppo, and Kiecolt-Glaser, 1996). Presumably, many of the benefits achieved through social support are due to dampened responses to stress. In the laboratory, social support appears to blunt HPA axis responses to psychological stressors in humans (Kirschbaum, Klauser, Filipp, and Hellhammer, 1995; Thorsteinsson and James, 1999). Furthermore, a meta-analysis of 22 clinical studies indicates that manipulating social support significantly affects cardiovascular and corticosteroid responses to laboratory stressors (Thorsteinsson and James, 1999). Blunted HPA axis responses to a novel environment also have been reported in socially bonded female guinea pigs (Sachser, Durschlag, and Hirzel, 1998). The type of stressor, however, may be an important factor in determining the effect of a social partner on the stress response. For example, introduction of a novel male into the home cage of pair bonded Siberian dwarf hamsters results in an augmented cortisol response and increased fighting as compared to when a novel male is introduced into the home cage of an unpaired cohort (Castro and Matt, 1997a). Presumably, the exaggerated physiological and behavioral responses to an intruder reflects the importance of mate guarding in a pair bonding species. Finally, the phenomenon of social buffering of stress responses is probably limited to species in which animals naturally live in pairs or communal groups. It would be unlikely for an individual of a solitary species to derive a similar benefit from paired housing (Sachser et al., 1998).

### HPA ACTIVATION INFLUENCES ON HEALTH AND DISEASE

Among the general public, it is commonly believed that stress and social isolation are important factors in the etiology of many diseases including stroke, cardiovascular disease, and cancer (House, Dennis, Mogridge, Hawton, and Warlow, 1990). Several clinical and experimental studies have provided evidence that elevated peri-ischemic concentrations of corticosteroids exacerbate stroke outcome (DeVries, Joh, Bernard, Hattori, Hurn, Traystman, and Alkayed, 2001b; House et al., 1990; Koide, Wieloch, and Siesjo, 1986; Murros, Fogelholm, Kettunen, and Vuorela, 1993; Olsson, Marklund, Gustafson, and Nasman, 1992). In most cases, however, rather than killing neurons directly, exposure to high concentrations of corticoste-
roids impairs the ability of neurons to recover from other forms of injury (Sapolsky and Pulsinelli, 1985). Suppressing bcl-2 expression in injured brain is an example of one mechanism through which stress, and presumably corticosteroids, may indirectly lead to increased neuronal death. Typically, bcl-2 proto-oncogene expression is low in adult brain but increases in a region specific manner following neuronal injury (Alkayed, Goto, Sugo, Joh, Klaus, Hu, Crain, Bernard, Traystman, and Hurn, 2001). Increased bcl-2 expression promotes cell survival and protects against apoptosis and cellular necrosis in numerous neurodegenerative disorders (Bergeron and Yuan, 1998). Recently, we demonstrated that extrinsic factors, such as chronic social intimidation and stress, can suppress bcl-2 expression in brain and exacerbate experimental stroke outcome. Stressed mice express approximately 70% less bcl-2 mRNA post-stroke and develop infarcts that are approximately four times larger than in unstressed animals. Transgenic mice that constitutively express excess bcl-2 are protected from stress-induced exacerbation of stroke infarct volume despite blood corticosteroid concentrations that are comparable to stressed wild type mice (DeVries et al., 2001b). Exposure of mice to social stress or exogenous CORT for several days prior to inducing stroke also results in increased neuronal death and exacerbated memory impairment (DeVries, Hattori, Morahan, Traystman, and Hurn, in press).

Positive social interaction can partially ameliorate the cognitive and histological damage induced by experimental stroke in male mice (Hattori, Hurn, Traystman, and DeVries, 2000). Males that are housed with ovariectomized females have smaller infarct volumes and less cognitive impairment than individually housed controls. Whether social pairing improves stroke outcome by suppressing peri-ischemic corticosteroid secretion and increasing bcl-2 expression remains to be determined. In a similar study, socially housing spontaneously hypertensive rats preserves sensorimotor function after stroke, but does not alter histological outcome (Johansson, 1996; Johansson and Ohlsson, 1996). Even delaying transfer into a socially enriched environment until after stroke is beneficial (Johansson, 1996). Social support also has been identified as an important factor affecting recovery in human stroke patients (Wyller, Holmen, Laake, and Laake, 1998). Despite the growing evidence that social and environmental factors can influence functional outcome after several different types of experimental brain injury (Held, Gordon, and Gentile, 1985; Johansson, 1996; Kolb and Gibb, 1991; Ohlsson and Johansson, 1995; Rosenzweig, 1984), the mechanisms through which social interaction and enriched environment improve functional outcome are not known.

**OXYTOCIN EFFECTS ON THE HPA AXIS**

Oxytocin (OT), a hypophyseal peptide hormone, is probably best known for its role in triggering uterine contractions during birth and initiating milk let-down in lactating females. In addition, OT is released in response to physical contact and vaginocervical stimulation during mating (reviewed in Carter, 1998). OT has also been identified as a potential regulator of the HPA axis.

Chronic treatment of females rats with OT results in a transient increase in CORT that is followed by long-term HPA axis suppression (Peterson, Hulting, and Uvnas-Moberg, 1999). Similarly, a single intracerebroventricular injection of OT in male and female prairie voles causes a rapid decline in CORT concentrations that resembles the decline observed following pairing of an unfamiliar male and female (DeVries and Carter, 1997). In contrast, intracerebral infusion of a selective OT antagonist increases basal and stress-induced CORT concentrations in rats of both sexes, presumably by releasing the HPA axis from OT-induced suppression of CRF release in the paraventricular nucleus of the hypothalamus (Neumann, Wigger, Torner, Holsboer, and Landgraf, 2000). Pharmacological studies in men suggest that OT also suppresses HPA axis activity at the levels of the pituitary and adrenal glands. (Chiodera and Coiro, 1987; Legros, Chiodera, and Geenen, 1988). Furthermore it appears that the effects of OT on the HPA axis may be mediated via an opioid dependent pathway because pretreatment with an opioid antagonist abolishes the effect of OT on corticosteroid concentrations (Cohen, 1988).

Lactation studies provide additional indirect evidence for the suppressive effects of OT on the HPA axis. Suckling in lactating women and breast stimulation in nonlactating women produces an increase in plasma OT and a decrease in ACTH and cortisol (Amico, Johnston, and Vagnucci, 1994; Chiodera, Salvarani, Bacchi-Modena, Spallanzani, Cigarini, Alboni, Gardini, and Coiro, 1991). In both women and rats, lactation attenuates stress-induced secretion of corticosteroids (Altemus, Deuster, Gallivan, Carter, and Gold, 1995; Lightman and Young, 1989). Exogenous OT also suppresses cortisol in lactating and nonlactating sheep (Cook, 1997). Furthermore, treatment of women with OT during parturition results in a significant decrease in blood ACTH and cortisol concentrations (Izzo, Rotondi, Perone, Lauro, Manzo, Casilli,
Rasile, and Amato, 1999). Although some studies have failed to report an effect of OT on HPA activity (Lewis and Sherman, 1985; Pfister and Muir, 1989), or have reported that OT is an ACTH secretagogue (Gibbs, Vale, Rivier, and Yen, 1984), the majority of studies suggest that OT exerts an inhibitory influence on HPA axis activity under a wide range of physiological and pharmacological conditions.

OT is a behaviorally active hormone that has been shown to affect social bonding, reproductive behavior, maternal behavior, aggression, anxiety, and memory (Carter, 1998). However, the extent to which OT-induced behavioral effects are the result of suppressed HPA axis function remains to be determined. Certainly, manipulations that increase OT or decrease corticosteroid concentrations appear to have very similar effects on partner preference in female prairie voles (Carter, 1998; Cho et al., 1999; DeVries et al., 1995; Williams et al., 1994) and sexual receptivity and lordosis in female rodents (Cushing and Carter, 1999; deCatanzaro, Knipping, and Wigmore, 1983). Taken together, these data suggest that there may be overlap in the proximate regulation of some behaviors by OT and HPA axis hormones. Furthermore, the release of OT during physical contact provides a mechanism through which social interaction can provide a buffer against stress and ultimately improve health and well-being.

SUMMARY

Involvement of the HPA axis in bond formation provides a mechanism through which social and environmental cues can influence social structure. Once a stable social bond has been established, positive social interactions may result in a buffering against some types of stressors. This observation forms the basis of a wide range of social-bonding phenomena including the positive effects of pet visitation to nursing homes (Counsell, Abram, and Gilbert, 1997), the importance of friendships and social networks for surviving cardiovascular disease and accidents (Kawachi, Colditz, Ascherio, Rimm, Giovannucci, Stampfer, and Willett, 1996), and the positive effects of marriage on longevity (Tucker, Friedman, Wingard, and Schwartz, 1996). The mechanism through which social bonds improve health and well-being is not known but may involve OT-induced suppression of the HPA axis.

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