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Physiology & Behavior 79 (2003) 399–407

PHYSIOLOGY & BEHAVIOR

Social modulation of stress responses

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Received 4 April 2003; accepted 17 April 2003

Abstract

Social interactions can profoundly affect the hypothalamic–pituitary–adrenal (HPA) axis. Although most research on social modulation of glucocorticoid concentrations has focused on the consequences of exposure to stressful social stimuli, there is a growing body of literature which suggests that social support in humans and affiliative behaviors in some animals can provide a buffer against stress and have a positive impact on measures of health and well-being. This review will compare HPA axis activity among individuals for whom social relationships are maintained through aggressive displays, such as dominance hierarchies, vs. individuals engaging in high levels of prosocial behavior. We also will examine oxytocin, a neuropeptide that is well known for promoting social behavior, as the physiological link between positive social interactions and suppression of the HPA axis. Despite many examples of social interaction modulating the HPA axis and improving health outcomes, there is relatively little known regarding the underlying mechanisms through which social behavior can provide a buffer against stress-related disease.

Keywords: Stress; Glucocorticoids; Oxytocin; Dominance; Behavior

1. Introduction

Depending on the circumstances, social interactions can be a source of stress or provide a buffer against stress. To date, most empirical studies of social influences on stress have focused on the negative, stress-inducing aspects of social interaction. Indeed, there remains little doubt that chronic exposure to psychosocial stress alters hypothalamic–pituitary–adrenal (HPA) axis function and compromises physical and mental health in humans and other animals [1,2]. Social stress has been identified as an important factor in the pathogenesis of disease. In mice, chronic social stress is associated with reactivation of latent herpes simplex virus type 1 [3] and increased susceptibility to bacterial endotoxic shock [4]. Social stress also increases susceptibility of rhesus monkeys (*Macaca mulatta*) to simian immunodeficiency virus (SIV) [5]. Those monkeys housed in unstable social groups are exposed to more aggression, engage in fewer affiliative behaviors, and ultimately survive a shorter time period compared to monkeys housed in stable social groups [5]. Receipt of aggressive threats is associated with a higher concentration of plasma SIV RNA while participation in affiliative behaviors, such as grooming, is associated with lower concentrations of SIV RNA [5]. Exposure to social stress also exacerbates noninfectious conditions. For example, social stress or treatment with exogenous corticosterone increases neuronal death and impairs functional recovery from stroke in mice [6,7]. Exposure to stress in utero may even predispose individuals to later stress-related disease. Retrospective studies in humans suggest that stress-induced HPA axis hyperactivity during pregnancy is associated with a predisposition toward schizophrenia and depression in adulthood [8].

Increasing evidence suggests that social support in humans and affiliative behaviors in some animals can have a positive impact on health and decrease mortality from many different causes [9,10]. For example, men who receive verbal support from a long-term "girlfriend" during a psychologically stressful period have lower cortisol concentrations than men who receive similar support from a stranger or receive no support [11]. Social support and affiliation also affect disease course in human [12] and nonhuman primates [5]. Level of social support is signifi-

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doi:10.1016/S0031-9384(03)00152-5

cantly correlated with rate of progression from asymptomatic to symptomatic stages of human immunodeficiency virus (HIV) infection in men [12]. Furthermore, stressful life events and high serum cortisol concentrations are associated with faster progression to acquired immune deficiency syndrome (AIDS) in HIV positive men [12].

Despite many examples of social interaction modulating the HPA axis and improving health outcomes, very little is known regarding the mechanisms through which social interaction effects these changes [10]. The purpose of this review is to describe how positive and negative social interactions can evoke HPA axis activity. We will also examine oxytocin as one of the physiological mechanisms through which positive social interactions suppress the HPA axis and improve health.

2. What is stress?

Activation of the HPA axis is one of the most thoroughly characterized neuroendocrine responses to stress. In fact, the three primary hormones of the HPA axis, corticotropin releasing factor (CRF), adrenocorticotropin hormone (ACTH), and cortisol (or corticosterone) are often referred to as ''stress'' hormones. However, even under nonstressful conditions, the hormones of the HPA axis play an important role in maintaining homeostasis and the proper energetic balance [13]. In addition, there is a strong circadian rhythm in HPA activity; peak hormone concentrations in the blood generally precede the onset of the animal's active phase, while the trough in hormone concentrations occurs during the inactive phase [14]. Proper regulation of the HPA axis via ''negative feedback'' allows the body to respond to acute energetic demands while minimizing long-term exposure to high concentrations of corticosteroids, which can have deleterious consequences [13].

The term ''stress'' was originally borrowed from the fields of physics and engineering to describe the biological state of disrupted homeostasis [15]. Although this term has become part of the vernacular, no consensus has yet been achieved for a precise definition of biological stress in the scientific literature [16]. Often, elevated concentrations of HPA axis hormones (specifically CRF, ACTH, and corticosterone or cortisol) are used as indices of stress and any stimulus, whether physical or psychological, that causes an increase in HPA axis activity is identified as a stressor. Indeed, within a short time of exposure to a stressor there is a measurable increase in the release of CRF from the hypothalamus, which in turn causes the release of ACTH from the anterior pituitary gland. ACTH then stimulates the release of glucocorticoids (corticosterone or cortisol) from the adrenal cortex [13].

Formal studies of stress, particularly those pertaining to biomedicine, have focused primarily on the pathological or maladaptive consequences of stress or activation of the HPA axis. Thus, the state of stress has acquired a negative connotation. In many cases, however, the so-called stress responses are initially adaptive responses that enable organisms to respond to changes in their environment [16]. The pathological consequences of stress typically occur after prolonged exposure to the stressor or mediators of the stress response, such as hormones of the HPA axis (reviewed in Ref. [17]). Thus, a stressful social environment can have deleterious consequences if the animal is exposed to chronically elevated corticosteroid concentrations. Conversely, in some species, positive social contact can provide homeostatic control of the HPA axis and may ultimately improve health and well-being by minimizing glucocorticoid exposure over time [18].

3. The relationship between social status and HPA activity

Animals that live in social groups or in close proximity to animals of their own species (and sometimes other species) often establish dominance relationships or social hierarchies. Stable social hierarchies serve to minimize within group aggression and competition [19]. However, the costs and benefits of defined social rank are not uniform across group members or species. Often, the dominant animals enjoy preferential access to limited resources such as mates and food. The dynamics of the hierarchy also may impact the frequency and types of social behaviors that are exhibited. For example, dominant male baboons tend to engage in more affiliative behavior with females and infants than subordinate males [20], which may contribute to lower basal cortisol concentrations in the high-ranking male baboons compared to subordinate males. Typically, dominant animals also initiate aggressive interactions more often than subordinate animals [21]. However, dominant animals may spend a greater amount of time in aggressive encounters than subordinate animals if they belong to a species that tends to form unstable hierarchies that are frequently challenged [21]. Thus, the level of stress associated with being a dominant vs. subordinate animal varies across species and may be related to the behavioral styles of the dominant animals and the level of social stability [21,22].

3.1. Factors that influence the relationship between social dominance and the HPA axis

3.1.1. Stability of social hierarchy

The relationship between social status and HPA axis activity in free-living mammals has been studied most extensively in olive baboons (*Papio cynocephalus*). Female olive baboons inherit social rank from their mothers and tend to remain within one troop for their entire lives. In contrast, young males tend to leave their natal group and immigrate to a nearby troop. Typically, the immigration process is associated with increased aggressive encounters [23]. In one olive baboon population, immigration of an

aggressive male caused an increase in mean cortisol concentrations of established group members. However, cortisol concentration was not directly related to the number of aggressive attacks received by an individual [24]. Furthermore, circulating cortisol concentrations of the immigrating male were consistently in the top quartile of the population under study [24]. Taken together, these data suggest that the immigration period may be stressful for both the immigrating male and the members of the group that he is joining.

During periods of relative social stability, dominant male baboons exhibit lower baseline cortisol concentrations, but larger stress-induced increases in cortisol concentrations compared to subordinate baboons [25]. Studies examining HPA axis negative feedback regulation in dominant and subordinate olive baboons suggest that hypercortisolemia in the subordinate animals results from dysregulation of the HPA axis at the level of the central nervous system [26,27]. The cause of the dysregulation has not been determined, but may be the result of chronic social subordination and ineffective coping strategies. High-ranking olive baboons are exposed to less aggression and have more ''control'' over aggressive encounters than subordinate males [28]. Presumably, because the dominant baboons initiate most of the aggressive encounters, they also have the psychological advantage of being able to predict the onset of the aggressive encounters [28]; (see Ref. [29] for discussion of importance of control, predictability, and outlets on corticosteroid responses to stress). Subordinate males tend to be socially isolated as well, which may have implications for their high level of HPA axis activity. Animals in the population that rate above the median in social connectedness (based on eight measures of affiliative behavior) have lower circulating cortisol concentrations than animals that rate below the median in social connectedness [28].

Social instability alters the relationship between cortisol concentration and dominance rank in rhesus monkeys as well. Low-ranking female rhesus monkeys in an established group have higher cortisol concentrations than high-ranking females [30]. In contrast, there is no relationship between cortisol concentration and dominance rank in a newly formed and relatively unstable hierarchy [30]. An interesting behavioral difference between the established and newly formed groups is that the monkeys in the newly formed groups engage in increased amounts of post-aggression reconciliatory behaviors, which may relieve some of the stress associated with losing a fight and ultimately result in low basal cortisol concentrations in both dominant and subordinate monkeys [30]. Reconciliation may be a behavioral strategy that the aggressors use to ease tensions in unstable social groups in which strong social alliances have not yet been established [30]. In contrast to female rhesus monkeys, a small study using males reveals no relationship between dominance rank and cortisol concentration [31].

Male cynomolgus monkeys (*Macaca fascicularis*) are another example of a species in which social stability influences the relationship between cortisol concentration and dominance rank. When they are housed with the same group of animals for approximately 15 months there is no significant difference in cortisol concentration between dominant and subordinate monkeys [32]. In contrast, when social instability is induced by rotating new animals into the group every month, the subordinate monkeys have higher cortisol concentrations than dominant monkeys and exhibit less aggressive behavior [32].

Social stability also can influence cortisol concentrations in rodent species. Dominant male and female naked mole-rats (*Heterochephalus glaber*) have significantly higher cortisol titers than subordinate colony members during periods of social stability [33]. In this eusocial species, dominance also is associated with increased body weight, aggressive behavior, and testosterone titers relative to subordinate animals [33]. The only reproductively active animals in the colony are the ''queen'' and as many as three high-ranking males. Removal of the queen induces social instability in both sexes and results in increased aggressive behavior and cortisol concentrations among colony members. During such periods of social instability, there is no longer a significant correlation between social rank and cortisol [33].

3.1.2. Behavioral strategies

As reviewed above, dominant male baboons in stable communities tend to have lower cortisol concentrations than subordinate males. Among the high-ranking male baboons, there are subpopulations of ''low cortisol'' individuals that exhibit one of two effective behavioral strategies [20,34]. The first subpopulation consists of males that engage in high levels of positive social interaction, particularly with females and infants. Presumably, the positive social interaction suppresses the HPA axis and decreases basal cortisol concentrations. The second subpopulation consists of males that appear to be socially astute regarding interactions with other males and are able to discriminate between challenges and neutral interactions. Likewise, this second subpopulation of dominant animals frequently uses outlets for frustration (for example, displacement of aggression on lower ranking individuals). The authors of the study suggest that rather than being a marker for dominance, low baseline cortisol concentrations are more closely correlated with behavioral traits that may affect outcome of a dominance interaction [34]. There also appears to be subpopulations of subordinate males with behavioral and physiological characteristics that differ from the typical subordinate population values [25]. For example, subordinate males that later join the dominant cohort are more likely than life-long subordinates to engage in overt consortships with receptive females (which often elicits aggression from dominants). The consorting males have higher basal cortisol concentrations and larger stress-induced cortisol responses than other subordinate males [25]. Another subset of subordinate males, who initiate fights or displace aggression afterwards, have relatively low cortisol concentrations [25]. Together, these

studies suggest that olive baboons exhibit a variety of behavioral styles and coping strategies and that these behavioral traits may impact both social rank and cortisol concentrations [20,25,34].

Dominant African wild dogs (*Lycaon pictus*) also tend to exhibit dimorphic behavioral and endocrine patterns in captivity [35]. A passive dominance style (low levels of aggression and high levels of affiliative behavior) is associated with low cortisol concentrations, whereas an active dominance style (high levels of aggressive behavior) is associated with high cortisol concentrations. The authors of the study suggest that an active dominance style is more stressful for the dominant animals than a passive dominance style because the repeated aggression implies an insecure social position that requires frequent demonstration of dominance [35]. However, the social dynamics of free-living and captive African wild dogs may be different because unconfined subordinate animals can often avoid or escape an attack more easily than those living in an enclosure [21]. Thus, in their natural habitat, dominant African wild dogs are involved in more aggressive interactions than subordinates [21] and have higher basal fecal corticosterone concentrations than subordinates [21]. On the whole, these data suggest that confinement may significantly alter the dynamics of a social hierarchy and ultimately affect the relationship between cortisol concentrations and dominance rank. Indeed, confinement has been shown to cause a fivefold increase in aggression related injuries in free-ranging rhesus macaques (*Macaca mulatta*; [36]).

3.1.3. Sex

The relationship between corticosteroids and social status can be sexually dimorphic. In dominant, free-living female dwarf mongooses (*Helogale parvula*) urinary basal and stress-induced cortisol concentrations are higher than in subordinate females [21]. In contrast, social rank is not correlated with basal hormone concentrations in male mongooses, but dominant males exhibit significantly lower cortisol responses to stress than subordinate males [21]. Another example of sexual dimorphism involves talapoin monkeys (*Miopithecus talapoin*). Dominant females have higher circulating cortisol concentrations and engage in more aggressive interactions than subordinate females [37]. However, when individually housed, previously dominant and subordinate female monkeys have similar blood cortisol concentrations, which suggests that elevated cortisol concentrations in dominant females are observed only in a social context [37]. In male talapoin monkeys, cortisol concentration is correlated with dominance rank, but it is the subordinate monkeys that receive the majority of the aggressive attacks and have the highest cortisol concentrations [38]. Thus, sexually dimorphic behavioral patterns may lead to a sexually dimorphic relationship between corticosteroid concentrations and social status.

3.1.4. Aggressive behavior

Two additional factors that emerge as important influences on the relationship between corticosteroids and social dominance are the frequency and social orientation of aggressive interactions. When subordinate animals bear the brunt of the aggressive attacks they tend to have higher cortisol concentrations than the dominant animals (for example, olive baboons; [25]), whereas when most of the aggressive interactions involve two dominant animals, their cortisol concentrations are typically higher than subordinates (for example, African wild dogs; [21]). However, even within a single population, the relationship between social dominance and corticosteroids may change as social conditions destabilize. For example, dominant male olive baboons typically have lower circulating cortisol concentrations than subordinate males [27]. In spite of this, if the dominant male is killed or disabled and there is no apparent heir, aggressive interactions between several high-ranking males will escalate and may continue for months. As a result, the high-ranking males become hypercortisolemic relative to previous years and their baseline and stress-induced cortisol concentrations begin to resemble subordinate baboons [27]. Thus, it appears that cortisol concentrations are low in dominant olive baboons only when they control the frequency, timing, and direction of aggressive interactions. However, it is important to note that even in the absence of frequent aggressive interactions some animals exhibit status-specific corticosteroid responses. Namely, rats spend relatively little time ($<1\%$) actually engaged in aggressive encounters following the establishment of a social hierarchy, but subordinate rats continue to exhibit submissive behaviors and have high circulating corticosterone concentrations relative to dominant rats long after aggressive interactions have ceased [39].

3.1.5. Culture among humans

Few studies have examined cortisol concentrations in the context of social status in humans. One such study involving Dominican men reported that those who were well regarded and behaved within the expected social norms had significantly lower basal cortisol concentrations than men who were rated by others as being disagreeable, untrustworthy, socially inappropriate, or without influence in the community [40]. In that study, economic and educational factors were not correlated with cortisol concentrations [40]. However, wealth and education correlate with cortisol concentrations in people from an industrialized society, which suggests that the influence of these two factors on HPA axis activity may be culturally mediated [41].

3.2. The relationship between HPA activity and social status: correlational or causal?

The relationship between circulating corticosteroids and social status in mammals varies greatly across species and is not always easily predicted based on behavioral observation.

One limitation in understanding the relationship between corticosteroid concentration and dominance rank is that most studies examine the degree of correlation between these two factors without addressing causality. Thus, it is not clear whether social status alters corticosteroid concentrations, corticosteroid concentrations alter social status, or if these two factors covary but do not directly influence one another. On the whole, the dominance data suggest that change in rank usually precedes change in cortisol concentrations [22]. However, there are a few examples of cortisol concentrations predicting future social rank. For example, in common marmosets (*Callithrix jacchus jacchus*) cortisol concentrations are predictive of social status upon group formation in the laboratory [42]. Female marmosets that have low morning cortisol concentrations are more likely to become dominant upon group formation, but once the group stabilizes, cortisol concentrations are similar in dominant and subordinate females [42]. In contrast, elevated morning cortisol concentrations are predictive of later subordinate status in pair-housed male marmosets [42]. Cortisol concentration also is predictive of the outcome of struggles for social dominance in male vervet monkeys (*Cercopithicus aethiops*). Baseline cortisol concentration is not related to dominance rank in stable colonies, but once social instability is induced, high cortisol concentration is predictive of future dominance [43].

4. Effects of prosocial behavior on the HPA axis

As noted, most studies examining the influence of social interactions on the HPA axis have focused on the role of aggression as the primary behavioral factor influencing corticosteroid concentrations. However, even in dominance hierarchies, which tend to be maintained through aggressive displays, there is evidence that positive social interaction may modulate HPA axis function [25,28]. Social buffering of stress responses has been extensively studied in the context of mother–infant bonding (reviewed in Ref. [18]); the present review will focus on adult social bonds as modulators of the HPA axis.

Social bonds are hypothetical constructs, and as such cannot be measured directly. However, there are several behavioral and physiological measures that have been used as indices of social bonding, including increased proximity [44], behavioral distress, or elevated corticosteroids following separation from the social partner [45–49]. Subsequent reunion with the partner should ameliorate the separation distress [50]. Although the behavioral and physiological markers of social bonding may vary across species, ultimately the attachment should facilitate reproduction and/or reduce levels of stress and anxiety [51]. In the laboratory, social support suppresses cortisol responses to psychological stressors in humans [11,52]. A meta-analysis of 22 clinical studies indicates that providing social support significantly decreases cardiovascular and corticosteroid responses to laboratory stressors [52]. Blunted HPA axis responses to a novel environment have also been reported in socially bonded female guinea pigs [53]. Furthermore, female black tufted-ear marmosets (*Callithrix kuhli*) that are removed from the natal family group and housed alone in a novel environment exhibit a significant increase in cortisol concentration unless housed with a familiar sibling upon separation from the rest of the family [54]. Socially isolated female squirrel monkeys (*Saimiri sciureus*) also have higher basal and stress-induced circulating cortisol concentrations than pair-housed monkeys [55]. Similarly, several laboratory rodent species have lower basal corticosterone concentrations and are less reactive to stress when housed in groups than when housed alone [56–58]. Physical contact through grooming and other affiliative behaviors is probably the most important aspect of the social housing. Indeed, stroking the abdomen of rats decreases their sympathoadrenal activity, increases vagal nerve tone, and increases oxytocin (OT) concentrations in plasma and cerebrospinal fluid [59]. Whether this stroking phenomenon generalizes to other forms and loci of physical contact, such as occurs during grooming, remains to be determined.

Thus, social suppression of the HPA axis has been documented in several species, including humans, and may profoundly affect well-being [60]. Conversely, even within a social species, there tends to be individual differences in the propensity to seek out affiliative interactions [25]. There also are circumstances under which having a social partner present may exacerbate stressful situations. For example, introduction of a novel male into the home cage of pair bonded Siberian dwarf hamsters (*Phodopus sungorus*) 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 [61]. Presumably, the exaggerated physiological and behavioral responses to an intruder reflect the importance of mate guarding. Thus, the type of stressor may be an important factor in determining the effect of a social partner on the stress response. Lastly, the beneficial effects of social buffering are probably limited to species in which animals naturally live in pairs or communal groups. It is unlikely that an individual of a solitary species would respond positively to forced social interaction [53].

5. Possible mechanism underlying social buffering of the HPA axis

A large body of clinical and experimental literature suggests that positive social interactions can have a profound effect on health [62]. Many of the benefits achieved through social support or affiliation are thought to result from suppressed HPA axis activity [11,52,63]. However, relatively little is known about the physiological mechanisms through which positive social interactions suppress corticosteroids [10,62]. One potential mechanism may in-

volve OT, a neurohypophysial hormone that has been shown to modulate both affiliative behaviors and the HPA axis (see Fig. 1).

OT is a behaviorally active peptide hormone that is probably best known for its roles in mating, parturition, lactation, maternal behavior, and pair bonding (for reviews, see Refs. [51,64,65]). OT also is released in response to physical contact [51,66,67] and induces excessive grooming when injected into the brain [68]. Furthermore, treatment with OT has been shown to decrease anxiety [69], which may be an important feature in its ability to increase sociality and facilitate reproductive and parental behaviors. Specifically, in rats, OT concentration in the cerebrospinal fluid is positively correlated with social behavior [70]. In addition to being a behaviorally active hormone, OT also is associated with suppressed HPA axis activity under a wide range of physiological and pharmacological conditions. For example, nipple stimulation in lactating and nonlactating women is associated with an increase in plasma OT concentration and a decline in plasma ACTH and cortisol concentrations [71,72]. Lactation also attenuates ACTH, cortisol, and glucose responses to treadmill exercise in women [73]. The lactating women in this study breastfed their infants approximately 1 h prior to exercising so that basal OT concentrations would be similar between lactating and nonlactating women at the beginning of the stress protocol. In contrast, breastfeeding approximately 40 min prior to the Trier Social Stress Test (TSST) did not alter the women's endocrine or psychological responses to the stressor [74]. Speech preparation and delivery during the TSST caused equivalent increases in anxiety and plasma concentrations of ACTH and cortisol in lactating and nonlactating women [74]. However, in a similar study, women who breastfed their infants 30 min prior to the TSST exhibited a significant increase in plasma epinephrine, norepinephrine, and cortisol concentrations in response to the stressor, but their cortisol response was attenuated compared to lactating women who held, but did not breastfeed, their babies during the same time period [75]. The lactating women who were restricted from feeding their babies reported increased tension and restlessness, but did not have higher cortisol concentrations than the nursing mothers prior to the TSST [75]. Taken together, these clinical data suggest that lactation dampens HPA axis reactivity to physical stressors, but recent suckling is required to restrain HPA responses to psychological stressors. One similarity among all three clinical studies is the lack of a relationship between plasma OT and cortisol or ACTH concentrations. Thus, it is not likely that in humans lactation-induced suppression of the HPA axis activity is mediated via OT effects on the pituitary or adrenal glands. However, in rodents there is evidence that suckling increases extracellular OT concentrations in several brain regions including the paraventricular nucleus, supraoptic nucleus, and hippocampus [76]. Furthermore, central injection of exogenous OT suppresses the HPA axis in rats [51,77]. Thus, it remains possible that suckling-induced changes in central OT mediate the effects of lactation on stress reactivity.

Lactation also blunts HPA axis reactivity to several stressors in rats including white noise [78], elevated plus-maze [79], forced swimming [79,80], acute cold exposure [81], and lipopolysaccharide injection [82]. Furthermore, corticosteroid response to ether stress is inversely related to litter size [83]. Down-regulation of the HPA axis during lactation may be occurring at the levels of the hypothalamus or the pituitary gland. Neither acute stress [84], nor intra-

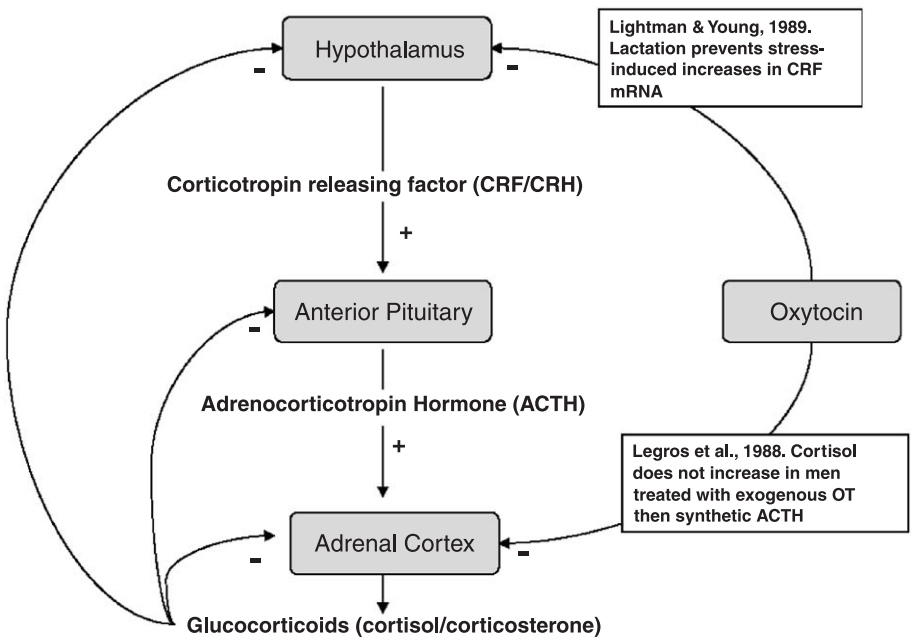

Fig. 1. Inhibition of the HPA axis by glucocorticoids and oxytocin.

cerebroventricular injection of a noradrenergic agonist [85] results in the expected induction of CRF mRNA in the paraventricular nucleus of lactating rats. Furthermore, ACTH response to administration of exogenous CRF is reduced in lactating rats compared to nulliparous controls [79].

An increase in OT secretion has been suggested as one mechanism through which lactation suppresses the HPA axis. Indeed, HPA axis hyporesponsivity can be achieved through central injection of OT in rats and prairie voles [51,77] and exogenous injection of OT in humans and other animals. In women, intravenous infusion of OT during parturition significantly decreases ACTH and cortisol concentrations [86]. Exogenous OT treatment also suppresses the HPA axis in males and nulliparous females. Female rats and hamsters that are chronically treated with exogenous OT exhibit a transient increase in serum corticosteroids [63,87,88], followed by a long-term suppression of the HPA axis [63,88]. Likewise, exogenous OT suppresses cortisol concentrations in sheep [89]. Pharmacological studies in men suggest that OT suppresses HPA axis activity at the levels of the pituitary and adrenal glands [72,90], which may explain why peripheral injections of OT are successful in suppressing the HPA axis [63,88]. The half-life of OT in plasma is very short (1–2 min) and it does not readily cross the blood–brain barrier [91,92]. However, others argue that when relatively large peripheral doses are used the 1–2% of the dose that does cross the blood–brain barrier is functionally significant [93].

Most of the research suggesting that OT restrains the HPA axis under natural conditions consists of correlational hormone data collected in lactating females. However, documented OT release during social interactions, including orgasm and nonsexual physical contact (reviewed in Ref. [51]), suggests a mechanism through which social support and affiliation may buffer the HPA axis in males and nonlactating females. Furthermore, the exogenous OT studies described above provide evidence that OT is capable of influencing HPA axis reactivity under a wide range of physiological and pharmacological conditions.

6. Conclusion

Social interaction profoundly influences HPA axis activity in humans and other animals. Psychosocial stress, or the lack of predictability and control over one's social environment, can lead to chronically elevated HPA axis activity and a deterioration of health [94–96]. In contrast, a wide range of social-bonding phenomena, including the positive effects of pet visitation to nursing homes [97], the importance of friendships and social networks for surviving cardiovascular disease and accidents [98], and the positive effects of marriage on longevity [99], support the hypothesis that positive social interaction can improve health and well-being. The physiological mechanism through which positive social interaction influences health is not known but may involve OT-induced suppression of the HPA axis.

Acknowledgements

We would like to acknowledge financial support from NINDS (RO1 NS40267-04) and a seed grant from the Stress and Wound Healing Center Grant at Ohio State University (NIDCR P50 DE13749). We also thank Tara Craft and Gretchen Neigh-McCandless for providing editorial comments.

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