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Salubrious effects of oxytocin on social stress-induced deficits

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Abstract

Social relationships are a fundamental aspect of life, affecting social, psychological, physiological, and behavioral functions. While social interactions can attenuate stress and promote health, disruption, confrontations, isolation, or neglect in the social environment can each be major stressors. Social stress can impair the basal function and stress-induced activation of the hypothalamic-pituitary-adrenal (HPA) axis, impairing function of multiple biological systems and posing a risk to mental and physical health. In contrast, social support can ameliorate stress-induced physiological and immunological deficits, reducing the risk of subsequent psychological distress and improving an individual's overall well-being. For better clinical treatment of these physiological and mental pathologies, it is necessary to understand the regulatory mechanisms of stress-induced pathologies as well as determine the underlying biological mechanisms that regulate social buffering of the stress system. A number of ethologically relevant animal models of social stress and species that form strong adult social bonds have been utilized to study the etiology, treatment, and prevention of stress-related disorders. While undoubtedly a number of biological pathways contribute to the social buffering of the stress response, the convergence of evidence denotes the regulatory effects of oxytocin in facilitating social bond-promoting behaviors and their effect on the stress response. Thus, oxytocin may be perceived as a common regulatory element of the social environment, stress response, and stress-induced risks on mental and physical health.

Keywords

Oxytocin; Immune system; Psychological distress; Social environment; HPA axis; Depression; Anxiety; Wound healing; Infections; Cancer

Introduction

Social relationships are a ubiquitous part of life, affecting social, psychological, physiological, and behavioral functions. Depending on the source and nature of the relationship, social interactions can promote or buffer against stress. Social stress is often a chronic or reoccurring aspect of the environment in humans and essentially all animal species and includes social disruption, confrontations, isolation, or neglect. Stressful social interactions or isolation can lead to a dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis that can result in systemic changes to physiological function that can manifest in

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stress-related diseases, disorders, and behavior. Selye (1936) first described this *non-specific response* as the *general adaptive syndrome*. For example, the negative effects of social isolation (including separation or loneliness) have been related to the incidence and symptomatology of depression, HPA axis dysfunction, stress-induced cardiovascular responses, delayed wound healing, and cancer mortality in humans (Franks and Moffatt, 2001; Steptoe et al., 2004; Dalgard et al., 2006; Kroenke et al., 2006; Grant et al., 2009; Sprehn et al., 2009; Carpenter et al., 2010). A number of social rodent and primate models have documented similar effects (e.g., Johnson et al., 1996; Shepherd & French, 1999; Detillion et al., 2004; Glasper and DeVries, 2005; French et al., 2007; Grippo et al., 2007a). Thus, understanding the social stress-induced disturbances on biological pathways may allow for improved clinical approaches toward treatment and prevention to abate the prevalence of these disorders.

Further, while stressful life events (e.g., divorce, death of a child or spouse, or job loss) are deleterious to mental and physical health (e.g., Garcia-Linares et al., 2004; Dalgard et al., 2006; Maulik et al., 2010), social support can ameliorate stress-induced biobehavioral responses in humans, reducing the risk of subsequent psychological disorders and improving well-being (Flannery and Wieman, 1989; Heinrichs et al., 2003; Smith et al., 1998; Maulik et al., 2010; recently reviewed in Insel, 2010; Karelina and DeVries, 2011). Therefore, as it is important to understand the regulatory mechanisms of stress-induced pathologies, it is equally relevant to determine the underlying biological mechanisms that regulate the social buffering effect to promote better clinical treatment of these physiological and mental pathologies and, ultimately, better health. Several animal models of social stress have been developed utilizing ethologically relevant conditions and species known to form strong adult social bonds to study the etiology, treatment, and prevention of stress-related disorders. While there are several biological pathways that undoubtedly promote the social buffering of the physiological and behavioral response to stress, there is burgeoning evidence that oxytocin seems to give impetus to social interactions and their effect on the stress response. Thus, oxytocin may be perceived as a common regulatory element of the social environment, stress response, and stress-induced risks on mental and physical health.

In the following review, we will describe the influence that stress in the social environment has on mental and physical well-being in humans and animals. Social stress during development, particularly on the parent-offspring bond, is associated with a negative impact to mental and physical health that is modulated by HPA axis function (reviewed in DeVries et al., 2007; Talge et al., 2007). In addition, humans and socially monogamous mammals develop stable, long-term male-female relationships in adulthood with strong social attachments (i.e., pair-bonds), defined by selective social behavior, and, in some species, biparental care (reviewed in Kleiman, 1977; Carter and Getz, 1993; Mendoza and Mason, 1997; Solomon and French, 1997; Young et al., 2011). Therefore, we will place a specific emphasis on human literature and animal models of adult social stress to understand the etiology and biological mechanisms of stress-related disorders induced by conditions in the social environment of adults. We will focus on the social stress-induced activation of the HPA axis as a major biological pathway that regulates these effects. In addition, we will describe how oxytocin causes and is affected by positive social interactions, and through oxytocin-mediated actions, the neuroendocrine, immune, and behavioral response to social stress are alleviated, promoting better health and well-being.

HPA axis and stress-related psychopathologies

From Selye (1950), a stressful stimulus causes disruption to normal homeostatic functions of the body and elicits a physical and physiological response. One of the primary biological pathways that respond to stress is the HPA axis, to the extent that the primary hormones of

this pathway – corticotrophin-releasing hormone (CRH), adrenocorticotrophic hormones (ACTH), and glucocorticoids – are referred to as stress hormones. The function of the HPA axis also includes actions that can be discrete from periods of stress or duress, such as sustaining homeostasis and metabolic balance (Sapolsky et al., 2000; Tasker, 2006). The activation of the HPA axis in response to a stressful event has been previously described, in detail (reviewed in Tsigos and Chrousos, 2002; Lightman, 2008). Briefly, the hypothalamic paraventricular nucleus (PVN) secretes CRH which moves through the hypophyseal portal blood and acts on the corticotroph cells of the anterior pituitary gland, increasing proopiomelanocortin transcription and releasing ACTH into the blood stream. ACTH subsequently acts on the adrenal cortex to release glucocorticoids, e.g., cortisol in humans and corticosteroids in rodents. Along with their role during stress responsivity, glucocorticoids can reduce HPA axis activity at the level of either the hypothalamus or pituitary in a negative feedback loop. An event or condition that results in a significant increase in the production and release of CRH, ACTH, and glucocorticoids is termed stressful. The activation of the HPA axis signals a cascade of physiological changes altering the perceived intensity and negative effects of stressful stimuli.

The innate function of the HPA axis is to arouse the system to changes in the environment, which can be adaptive during an acute response (e.g., mobilizing energy reserves during a predator attack: Sapolsky, 1998). Stress-induced mental pathologies are usually the result of repeated or prolonged stress, which is characteristic to stress derived from the social environment. The social stress-induced activation of the HPA axis seems to be a major pathway underlying many of these stress-related psychopathologies. Here, we review the evidence in humans to establish the relationship between social stress and mental diseases and disorders, focusing on depression and anxiety. Several animal models of social stress that utilize ethologically relevant conditions and species known to form strong social bonds will be discussed to outline the stress-induced activation of the HPA axis as a major biological pathway that underlying the manifestation of such pathologies. In contrast, social relationships can buffer against stress-induced effects on depression and anxiety via an oxytocin-mediated pathway. Therefore, we will discuss the effects that oxytocin has on alleviating and preventing the activation of the HPA axis and subsequent mental health problems.

Aversive effects of social stress

Stress in the social environment can lead to the emergence of psychological distress and a number of mental pathologies in humans such as major depressive disorder, generalized anxiety disorder, and panic disorder as well as alcohol or drug abuse or dependence disorder. There are a number of conditions in the social environment that results in stress-induced detriments to mental health in adulthood (e.g., Schulz et al., 2006; Dailey and Humphreys, 2011; Chou et al., in press). Here, we will focus on the impact of committed, intimate adult relationships on mental health, as this is one of the most significant relationships in humans, and several animal models highlighting potential biological mechanisms. Particularly, we will focus on the mental health detriments associated with marital status and changes to marital status as these measures are often proxy for the presence and nature of a significant social bond in adults.

Adult social relationships and mental health: The case for committed relationships

Social stress in adulthood can be debilitating to mental health and well-being, and no adult relationship is more important in humans than the one between significant others, which typically manifest as a strong social bond, stable social environment, an integral aspect of human social behavior. This close social relationship has been implicated in psychological health and well-being. Therefore, it is not surprising that when this social bond is lacking or

maladaptive, a number of stress-related mental pathologies may manifest. For example, compared to their married counterparts, single men and women who have never married not only report lower positive relations but also higher depression and hostility scores, more feelings of loneliness, and lower global happiness, life satisfaction, and self-acceptance scores (Marks and Lambert, 1998; Waite and Hughes, 1999; Mirowsky and Ross, 2003; Williams, 2003; Steptoe et al., 2004), all markers of increased psychological distress. Social loss and spousal bereavement also increase the risk for mental disease and disorders (Barrett, 2000; Carr et al., 2000; Carr et al., 2001; Wade and Pevalin, 2004). Notably, the risk for depression and anxiety can manifest before the death of a spouse (Williams et al., 2008) and last for decades afterward (Carnelley et al., 2006). Even temporary social separation can result in an increased perception of anxiety in men (Diamond et al., 2008). However, widowhood may be particularly stressful as it may be preceded by a period in which the deceased spouse was in poor health, reducing a source of social support and creating a source of stress. It should be noted that the negative effects of social isolation on mental health are not limited to heterosexual couples. Interestingly, a recent study noted that single gays and lesbians reported higher psychological distress (i.e., internalized homophobia, depressive symptoms, and stress) and a lower sense of well-being (i.e., the presence of meaning in life) than individuals in committed or legally-recognized same-sex relationships (Riggle et al., 2010). The quality and intimacy associated with heterosexual marriages are often not distinguishable from that which is observed in committed same-sex couples (Roisman et al., 2008). This may explain the fact that the lack of a strong social tie in humans that usually manifest in adults seems universally detrimental to mental health.

Getting married tends to improve mental health, reducing the risk of depression, anxiety, and substance abuse (Horwitz and White, 1991; Marks and Lambert, 1998; Simon, 2002). However, psychological distress can be increased in married individuals if the marital quality is poor due to strain, conflict, or abuse. The negative effects of marital strain or conflict may be more salient than the positive effects of marriage as individuals tend to dwell more on negative than positive encounters, repeatedly replaying them mentally (Taylor, 1991). Therefore, the tendency to worry over stressful social interactions could further impair psychological well-being in people during periods of marital conflict. Poor marital quality can culminate in divorce, and studies that examine marital change due to separation or divorce note a marked increase in depressive affect (Marks and Lambert, 1998; Simon, 2002; Wade and Pevalin, 2004). Some of these deficits may be attributable to social selection as healthy, well-adjusted individuals usually are attractive partners. Nevertheless, there is evidence that the lack of a significant adult social bond associated with a marriage or committed same-sex relationship directly leads to poorer mental health (e.g., Johnson and Wu, 2002). Divorce is a process beginning well before the discrete legal event, and therefore, the declines in psychological well-being associated with divorce can be due to the conflict within the marriage that precedes the divorce. Furthermore, even when divorce is desired, it can be stressful, and the social disruption associated with divorce may initiate a period of chronic stress associated with becoming a single parent, losing a source of emotional support, continued conflict with an ex-spouse, and economical decline (Williams and Umberson, 2004; reviewed in Amato, 2000).

Deficits in adult social bonds induce psychological and behavioral pathologies via a HPA axis-mediated mechanism

One of the major pathways in which social stress induces pathologies and behavioral consequences is the HPA axis. Numerous experiments in humans indicate an association between stress-induced activation of the HPA axis, particularly the release of its end product glucocorticoids, and increased psychological distress that can manifest in mental pathologies. For example, in traditional laboratory psychosocial stressors (e.g., Trier Social

Stress Test) and non-laboratory social stressors (e.g., temporary separation from a marital partner), the stress-induced cortisol response is associated with an increased perception of anxiety (Ditzen et al., 2007; Robles, 2007; Diamond et al., 2008). In clinical research, individuals with depression, anxiety, fear, and panic disorders often have dysregulated HPA axis activity, raised basal plasma cortisol, and more intense ACTH and cortisol responses to stress (Rothschild et al., 1989; Tse and Bond, 2004; Vreeburg et al., 2009; Vreeburg et al., 2010; reviewed by Papathanassoglou et al., 2010). A number of animal models of social stress have been developed to better understand the effects and function of the HPA axis and its stress hormones on social stress-induced psychopathologies.

In several socially monogamous New World rodents and primates, disruption to or absence of the close social bond that forms in male-female breeding pairs has been used to assess the HPA axis-mediated effects of social stress on mental pathologies. For example, individual housing can lead to an increased HPA axis and depression- and anxiety-like behavioral response to acute stressors (e.g., open field, elevated plus maze, forced swim, and sucrose preference tests) compared to social housing in monogamous rodents such as prairie voles (*Microtus ochrogaster*) (Stowe et al., 2005; Grippo et al., 2007a; Grippo et al., 2007b; Grippo et al., 2007c; Grippo et al., 2008; Grippo et al., 2009; Pournajafi-Nazarloo et al., 2009; Lieberwirth et al., 2011). In addition, when prairie voles lack a pair-bond, the rewarding properties of substances of abuse, such as amphetamine, are enhanced, even when they are housed with a same-sex conspecific (Liu et al., 2011; see Piazza and Le Moal, 1998 for a review on HPA axis-mediated substance use and abuse). Furthermore, social separation during periods of psychological distress can intensify the HPA axis and stress-related behavioral response. In our laboratory, we have recently observed that when pair-bonded female prairie voles experience an acute psychological stressor (e.g., immobilization stress), the stress-induced rise in corticosterone in circulation persists longer if they recover alone compared to recovery with their male partner (Smith and Wang, 2011). In addition, stressed female prairie voles that recover without their social partner express increased anxiety-like behavior during a heterotypic psychological stressor (e.g., elevated plus maze). Pair-bonded male prairie voles have elevated basal corticosterone levels and an increased depression-like response to acute psychological stressors (e.g., forced swim or tail suspension test) after experiencing a permanent, long-term separation from their female partner, but this is not true when males are permanently separated from a familiar male (Bosch et al., 2009). Furthermore, inhibition of the stress-induced activation of the HPA axis via a nonselective CRH receptor antagonist or selective CRH-1 or CRH-2 receptor antagonists can eliminate the depression-like response to acute psychological stressors that is induced by the loss of a female partner in pair-bonded male prairie voles (Bosch et al., 2009). It seems that disruption to or the absence of an adult social bond can impair mental health via the activation of the HPA axis.

Interestingly, the response to social isolation or separation from familiar conspecifics may depend upon the intensity of existing affiliative bonds between group members. In prairie voles, social separation from a same-sex conspecific does not seem to alter basal corticosterone concentrations, even during periods of isolation (Grippo et al., 2007a; Pournajafi-Nazarloo et al., 2009). However, basal corticosterone levels in circulation are higher in prairie voles housed with a same-sex conspecific compared to pair-bonded voles (Campbell et al., 2009). Further, exposing unpaired male and female prairie voles to an opposite-sex conspecific reduces basal corticosterone levels, but exposure to a same-sex conspecific does not (DeVries et al., 1995; Carter et al., 1997; DeVries et al., 1997). Thus, it seems that the stress-induced activation of the HPA axis and subsequent impairment of an individual's psychological well-being is dependent on the type of bond that is absent or disrupted. Thus, in humans and socially monogamous species in which the significant

relationship is between romantic or committed partners, deficits to this bond seem to be particularly damaging to mental health.

In some cases, HPA axis function, in particular glucocorticoid activity, can suppress the formation of pair bonds. For example, under short-term cohabitation (1 h), female prairie voles do not display a partner preference, a selective preference to interact with a familiar male over an unfamiliar male used as a laboratory index of the formation of a pair-bond (reviewed in Young et al., 2011). In contrast, a partner preference is displayed under long-term cohabitation (3 h or longer). However, if female prairie voles are adrenalectomized before a short-term cohabitation with a male, they display a partner preference, while corticosterone injections can inhibit partner preference formation in adrenalectomized females (DeVries et al., 1995). Furthermore, partner preference formation after a long-term cohabitation with a male is impaired in intact females exposed to a psychological stressor (e.g., forced swim test) or injected with corticosterone, but not adrenalectomized females (DeVries et al., 1995; DeVries et al., 1996). As adult social bonds can buffer from prolonged HPA activity and stress-related behavioral deficits in female prairie voles (e.g., Smith and Wang, 2011), impairing the formation of these bonds may be another mechanism through which stress-related psychopathologies may arise via a glucocorticoid-mediated pathway.

The absence of a pair-bonded partner also results in more anxiety-like behaviors and excited HPA axis function in socially monogamous primates such as marmosets (family: *Callitrichidae*) and titi monkeys (genus: *Callicebus*). Social isolation or separation from a bonded partner in marmosets increases basal cortisol, stress-induced cortisol response, anxiety-like behavior, and proximity seeking behavior (Johnson et al., 1996; Smith and French, 1997; Smith et al., 1998; Shepherd and French, 1999; Gerber et al., 2002; Gerber and Schnell, 2004; Rukstalis and French, 2005; French et al., 2007; Smith et al., 2011). The effects of social isolation or separation from the bonded partner are similar in titi monkeys (Mendoza and Mason, 1986b; Mendoza and Mason, 1986a; Hennessy et al., 1995; Fernandez-Duque et al., 1997). If the stress-induced activation of the HPA axis associated with separation from a long-term pair-bonded partner is inhibited by a CRH-1 receptor antagonist (e.g., antalarmin), the magnitude of the cortisol response and display of vocal distress and agitated- or anxiety-related behaviors are significantly reduced in marmosets (French et al., 2007). Thus, the physiological and behavioral manifestations of psychological distress associated with social separation seem to be mediated by the activation of the HPA axis. Interestingly, social isolation prior to the establishment of a new social pair increases proximity seeking behavior in marmosets, and this increase in proximity seeking behavior is associated with higher cortisol levels (Smith et al., 2011). As adult social bonds are a fundamental aspect of the social environment in humans and socially monogamous non-human primates and rodents, the absence of or interference with this bond may represent a major disturbance to the normal function and state of these animals leading to the activation of the HPA axis. If the stressful social environment persists, the HPA axis activity seems to become dysregulated leading to psychological and behavioral pathologies. In contrast, attachment behaviors and social contact increases an individual's sense of security, particularly in stressful periods in humans (Shear and Shair, 2005; Ravitz et al., 2010), and decreases the basal and stress-induced HPA axis activity in marmosets (Smith and French, 1997; Smith et al., 1998; Smith et al., 2011). Therefore, the increased proximity seeking behavior may be an adaptive response to social isolation to minimize the detrimental effects of this type of social stress. The formation and maintenance of social bonds may therefore result, in part, from the psychological distress associated with bond disruption or absence and the anxiolytic benefits of social interactions.

Protective effects of oxytocin

Stress in the social environment due to the lack of close social relationships in adulthood is maladaptive to mental health and well-being; however, social support, particularly from close social relationships such as a committed or pair-bonded partner, can reduce stress-induced behavioral and psychological manifestations (Maulik et al., 2010; Smith and Wang, 2011). For example, the occurrence of depression is significantly lowered in previously single men and women that marry for the first-time (Marks and Lambert, 1998). Substance abuse and the risk of relapse is markedly lower in individuals in committed, stable relationships in humans (Kosten et al., 1987). One reason social relationships and affiliative interactions may improve mental health is by reducing the HPA axis activity and psychological distress that is associated with a stressful life event or condition. For example, physical contact or verbal support from a committed partner or best friend can significantly lower cortisol concentrations during a psychologically stressful period compared to support from a stranger or no support in humans (Kirschbaum et al., 1995; Heinrichs et al., 2003). Social contact or housing also lowers basal and stress-induced glucocorticoid levels in animals that establish adult social bonds like prairie voles, marmosets, and titis (see previous section) as well as California and cactus mice (*Peromyscus californicus* and *P. eremicus*: Glasper and DeVries, 2005; Chauke et al., 2011), guinea pigs (*Cavia aperea f. porcellus*: Sachser et al., 1998; Kaiser et al., 2003; Adrian et al., 2008; Hennessy et al., 2008), and dwarf hamsters (*Phodopus sungorus* and *P. campbelli*: Castro and Matt, 1997; Reburn and Wynne-Edwards, 1999; Detillion et al., 2004). Interestingly, these social relationships both promote and are regulated by the oxytocin system (reviewed in Young and Wang, 2004; Young et al., 2005). In addition, oxytocin can directly attenuate the activation of the HPA axis and is associated with reducing the stress-induced psychological health risks. Thus, it is completely logical to speculate that oxytocin may mediate the social buffering of the stress response and subsequent psychological distress.

Evidence for an oxytocin-mediated mechanism of social buffering on stress includes research in humans and gregarious animals. Oxytocin appears to function as an anxiolytic, suppressing HPA axis function during periods of stress. Oxytocin released in the hypothalamus or exogenously administered attenuates activation of the HPA axis and reduces depression- and anxiety-like behavior during psychological stress (Legros et al., 1987; Windle et al., 1997; Petersson et al., 1999; Neumann et al., 2000; Heinrichs et al., 2003; Windle et al., 2004; Parker et al., 2005; Ditzen et al., 2009; Zheng et al., 2010; Linnen et al., 2011). For example, oxytocin is released in the PVN of male rats during mating with a receptive female and proceeded by reduced anxiety-like behavior during psychological stress, lasting at least 4 h after mating (Waldherr and Neumann, 2007). In addition, intracerebroventricular (icv) administration of oxytocin can reverse stress-induced social avoidance to follow social defeat in rats and mice (Lukas et al., 2011). Furthermore, social support following intense psychological stress (i.e., immobilization stress) can promote the release of oxytocin in the PVN while attenuating the physiological and behavioral stress response toward a subsequent stressor (i.e., elevated plus maze) in pair-bonded female prairie voles (Smith and Wang, 2011). Inhibition of oxytocin action in brain regions that release oxytocin during psychological stress (e.g., PVN: Bosch et al., 2004; Smith and Wang, 2011; central amygdala: Ebner et al., 2004) via site-specific or icv administration of an oxytocin receptor antagonist can attenuate the stress-induced physiological and behavioral response (Neumann et al., 2000; Ebner et al., 2004).

In humans, social relationships are also associated with activity of the oxytocin system. For example, higher plasma oxytocin levels are associated with more positive communication and physical contact between married couples (Turner et al., 1999; Grewen et al., 2005; Holt-Lunstad et al., 2008; Gouin et al., 2010). When interaction with a social partner is associated with elevated plasma oxytocin, it seems that blood pressure and heart rate is

lowered (Light et al., 2005). In addition, intranasal oxytocin administrations can reduce the cortisol response during couple conflict and promote positive communication (Ditzen et al., 2009). Further, social support attenuates the cortisol and subjective response (e.g., increases calmness and decreases anxiety) to psychosocial stress in humans, and intranasal oxytocin treatments can potentiate these effects (Heinrichs et al., 2003; Quirin et al., 2011). Conversely, oxytocin may serve as an index of relationship distress as women with perceived poor relationships or social networks can have elevated plasma oxytocin concentrations (Taylor et al., 2006; Taylor et al., 2010). Thus, as oxytocin seems to be an impetus for social interactions, oxytocin activity during relationship distress may facilitate social reconciliation or integration as an active coping mechanism. While the delivery route of intranasal oxytocin is not clearly understood or whether plasma oxytocin reflects central activity, the data in humans evaluating the dynamics between oxytocin, prosocial interactions, and the stress response seems to be consistent with more direct evidence from animal models. Therefore, it could be hypothesized that while social stress can promote psychological distress via the activation of the HPA axis, social support can attenuate these effects by marginalizing the HPA axis activity via activation of the central oxytocin system.

Several recent studies have provided more evidence that directly supports this speculated hypothesis. Most, if not all, mammalian species exist in an highly complex social environment, and social living often are critical to the fundamental aspects surrounding fitness, including reproductive success, predatory response, territory and resource allocation and defense, and offspring care (reviewed in Kleiman, 1977; Neumann, 2009). In species that display highly developed social structures, social interactions persist throughout daily life and can modulate the response to various stimuli including stress. Therefore, social stress can have profound effects on the mental state of humans and gregarious animals, particularly in the absence of social bonds. In several socially monogamous (e.g., hamsters and prairie voles) and gregarious (e.g., rats and mice) rodent species, social isolation is met with activation of the HPA axis that promotes depression- and anxiety-like behaviors (Detillion et al., 2004; Waldherr and Neumann, 2007; Grippo et al., 2009; Norman et al., 2010; Lieberwirth et al., 2011). However, if oxytocin is administered during social isolation, the increased basal and stress-induced activation of the HPA axis and the subsequent consequences to depression- and anxiety-like behavior are alleviated (Detillion et al., 2004; Grippo et al., 2009; Norman et al., 2010). For example, female prairie voles that are chronically isolated display higher depression-like behavior in response to psychological stress and symptoms of anhedonia (e.g., a diminished sucrose preference) compared to a period of social housing; however, if oxytocin is administered during social isolation, these depression-like symptoms are not observed (Grippo et al., 2009). Therefore, the negative impact of social isolation on the stress pathway and psychological or behavioral pathologies can be attenuated by oxytocin action. In two studies, the beneficial effects of social interactions were diminished by the inhibition of oxytocin action by an oxytocin receptor antagonist. Specifically, while mating can reduce anxiety-like behavior during psychological stress in male rats, the social buffering effect of mating can be inhibited by a central infusion of an oxytocin receptor antagonist (Waldherr and Neumann, 2007). In addition, social housing can prevent the development of depression-like behavior during psychological stress in mice with chronic pain, yet blockade of the receptor-mediated action of endogenous oxytocin inhibits the attenuation of depression-like behavior in socially-housed mice (Norman et al., 2010). These studies support the contention that the mental health-promoting effects of social relationship are regulated by the central oxytocin system.

Oxytocin-mediated social buffering localized in the PVN

The effects of social buffering as mediated by oxytocin may be localized within the PVN, as the suppressive effects of oxytocin on the HPA axis seems to be mediated within the PVN

itself. First, the production and release of oxytocin originates from the PVN (reviewed in Gimpl and Fahrenholz, 2001). Neurons within this region are sensitive to oxytocin, as indicated by alterations in the firing rates (Inenaga and Yamashita, 1986). In addition, there are synaptic contacts between oxytocin- and CRH-expressing neurons, and oxytocin receptors are colocalized on CRH-expressing neurons in the PVN (Hisano et al., 1992; Dabrowska et al., 2011). This provides a neuronal basis for a PVN-originating effect of oxytocin on the HPA axis activity. Second, oxytocin is released within the PVN in response to psychosocial stress and social interactions (Nishioka et al., 1998; Engelmann et al., 1999; Bosch et al., 2004; Smith and Wang, 2011), which includes dendritic release from intranuclear neurons (reviewed in Ludwig, 1998). Plasma oxytocin can act directly on the adrenal cortex to regulate the release of glucocorticoids (Legros et al., 1988). However, social stress can induce activation of the HPA axis and hypothalamic release of oxytocin without a reciprocal elevation in plasma oxytocin levels (Engelmann et al., 1999). Third, like social interactions, local oxytocin microinjections in this region can alter intracellular signaling in neurons, including CRH-expressing neurons. For example, stress-induced expression of immediate-early gene product Fos in CRH-expressing neurons in the PVN is inhibited by social housing (Kiyokawa et al., 2004) and local microinjections of oxytocin (Windle et al., 2004) in rats. In addition, intra-PVN oxytocin injections can promote local activation of the MAP kinase cascade, while blockage of MAP kinase signaling in the PVN by a MEK1/2 inhibitor can inhibit the anxiolytic effects of oxytocin (Blume et al., 2008). Finally, the stress-induced rise of plasma ACTH and corticosterone and anxiety-like behavior to acute psychological stressors are attenuated by microinjections of oxytocin in the PVN (Windle et al., 2004; Neumann et al., 2006; Blume et al., 2008).

Immune system and physical health

The immune response occurs in periods of physical risk such as injury, infection, or cancer (see Yates and Lyczak, 2004 for a basic review). This response originates in lymphoid organs (e.g., thymus, bone marrow, lymph nodes, spleen, tonsils, appendix, and Peyer's patches) and leads to the innate or adaptive actions of factors such as phagocytes and lymphocytes that identify and destroy foreign substances. With few exceptions, distress in the social environment can result in a suppressive immune response, while oxytocin can promote the body's immune defenses.

Aversive effects of social stress

There are a number of studies that have documented immunosuppressive effects during periods of social stress, influencing the response to injury, infection, and cancer. For example, individuals with few or weak social ties are more susceptible to viral infections, have weaker vaccine responses, and have a greater prevalence of reactivating latent viral infections (Glaser et al., 1985; Glaser et al., 1992; Cohen et al., 1997). In addition, patients with cancer have a diminished survival rate if they are socially isolated or separated from their spouse (Kroenke et al., 2006; Sprehn et al., 2009). Social isolation has also been associated with increased intratumoral catecholamine levels – which can act on β -adrenergic receptors on immune cells to alter their activity and increase tumor growth (Lutgendorf et al., 2011). This increase is associated with a greater disease severity in patients with ovarian carcinoma. However, social relationships can also be a source of stress, and stressful social interactions can negatively impact the immune response to injury and infection. For instance, a turbulent marriage can be a major social stressor and can concomitantly inhibit social support seeking in other relationships (reviewed in Kiecolt-Glaser and Newton, 2001). Couples experiencing periods of marital conflict have an impaired immune response to various herpes viruses and slower wound healing, regardless if they are newly-weds or long-term couples (Kiecolt-Glaser et al., 1993; Kiecolt-Glaser et al., 1997; Mayne et al., 1997; Garcia-Linares et al., 2004; Kiecolt-Glaser et al., 2005). In addition, family conflict (e.g.,

physical abuse, overcrowding, and social disruption or poor support) has been associated with impaired immune response to the Epstein-Barr virus in young Afghan women (Panter-Brick et al., 2008). Further, the stress that is associated with caring for and coping with a spouse or parent with Alzheimer's disease can result in immune suppression and negative health outcomes such as weaker vaccine response and delayed wound healing (Irwin et al., 1991; Castle et al., 1995; Kiecolt-Glaser et al., 1995; Kiecolt-Glaser et al., 1996; Mills et al., 1999). These effects can persist beyond the end of caregiving, especially if there is low social support (Kiecolt-Glaser et al., 1991; Glaser et al., 1998). The chronic stress associated with caregiving to a spouse with dementia is associated with a down-regulation of growth hormone expression in lymphocyte cells, which in turn can reduce B- and T-cell production and immune response to infections (Wu et al., 1999). In addition, stress slows the production of proinflammatory cytokines at the site of injury, providing mechanisms whereby wound healing would be delayed by experiencing social stress (Glaser et al., 1999). Clinical conditions have been useful in establishing a relationship between social stress and the immune response, though this relationship is only correlational. Auspiciously, the stress-induced effects on the immune system are similar between animals and humans. Therefore, stress-induced immunosuppression animal models have been developed to identify the biological mechanisms.

Stress-induced HPA activity affects immune function

The best-documented pathway in stress-induced immunosuppression is through a glucocorticoid-mediated mechanism. Primates and rodents have been used to establish models of clinical conditions and evaluate the effects that social stress has on the immune system. For example, social isolation induced an increase in corticosterone concentrations and delayed wound healing in dwarf hamsters, which form social bonds with familiar conspecifics (Crawley, 1984), unless hamsters were adrenalectomized (Detillion et al., 2004). In addition, social isolation and long-term separation induced similar effects on the HPA axis and wound healing in two monogamous mice species (*P. californicus* and *P. eremicus*), but not in a closely-related polygamous species (*P. leucopus*) (Glaser and DeVries, 2005). Treatment with a glucocorticoid receptor antagonist prior to a stressful experience and injury can inhibit the stress-induced delay to wound healing and inflammation at the wound site in mice (Padgett et al., 1998a). Dexamethasone and methylprednisolone (synthetic glucocorticoids) treatment delayed wound healing in rats and mice, reduced cytokine production in macrophages during wound repair in mice, and lowered basal lymphocyte cell population in rhesus monkeys (*Macaca mulatta*) (Suh et al., 1992; Gordon et al., 1994; Hübner et al., 1996; Cole et al., 2009). This is coupled with a stress-and glucocorticoid-induced suppression of pro-inflammatory cytokines and proangiogenic growth factors (e.g., interleukin (IL)-1, IL-8, platelet-derived growth factor, and macrophage inhibitory protein (MIP)-1 α), and cytotoxic T cells expression in the damaged and surrounding tissue in rodents and primates (Sei et al., 1992; Hübner et al., 1996; Mercado et al., 2002; Head et al., 2006; Kalin et al., 2006). Thus, the stress-induced glucocorticoid regulation of wound healing is likely via local immunosuppression at the wound site.

This delay in the inflammatory stage would also lead to a slower progression of the immune response into subsequent stages (i.e., proliferation and remodeling) (Hübner et al., 1996). In addition, the social stress-induced suppression of the inflammatory response and delay in proliferation and remodeling can expose wound sites to an increased risk of infectious disease. In fact, stress impairs bacterial clearance during wound healing, leading to a greater incidence of opportunistic infection (Rojas et al., 2002). Further, disruption to the established social hierarchies in male mice promotes a prolonged rise in corticosterone in circulation and subsequently reactivates a latent herpes simplex virus (HSV-1) infection a

month after inoculation compared to undisturbed controls (Padgett et al., 1998b). Social instability promoted an increase in simian immunodeficiency virus RNA in plasma after inoculation in male rhesus macaques (Capitanio et al., 1998) and reactivation of a latent lymphocryptovirus (also called Epstein-Barr virus chimpanzee) in male chimpanzees (*Pan troglodytes*) (Yamamoto et al., 2010). Thus, the social stress-induced HPA axis activity may down-regulate the immediate immune response to new infections and promote the physiological pathways required to reactivate latent infections. In addition, lymphocytes are more sensitive to glucocorticoid-induced suppression when at rest than during an immune response (Dennis et al., 1987; Luster et al., 1988). Thus, if a period of chronic social instability or isolation precedes an injury or infection, the elevated production of glucocorticoids could result in a weakened immune response, enhancing the risk for a more severe infection or prolonged recovery.

As noted by Godbout and Glaser (2006), the effects of social stress-induced activation of the HPA axis on reactivation of latent herpes virus also has implications for cancer progression as the Epstein-Barr virus is associated with nasopharyngeal carcinoma and African Burkitt's, non-Hodgkin's, and post-transplant lymphomas (Petrella et al., 1997; Ansell et al., 1999; Brousset, 2002; Tuitou et al., 2003). In addition, social loss and fighting leads to a reduction in cytotoxic T cell production and response in mice (Hardy et al., 1990; Sei et al., 1992). The social stress-induced decreases in circulating numbers of T helper cells, cytotoxic T cells, and B cells are abolished in adrenalectomized rats (Engler et al., 2004). Therefore, whether directly via glucocorticoid suppression of lymphoid cells that target abnormally growing cells for destruction or indirectly via promotion of latent herpes virus reactivation, the effects that social stress-induced glucocorticoid release has on the inflammation phase of the immune response could have implications on cancer progression and severity.

Protective effects of oxytocin

Social support improves the outcome from a wide variety of clinical conditions, including cancer (Levy et al., 1990; Spiegel and Sephton, 2001), systemic lupus erythematosus (Bae et al., 2001), and human immunodeficiency virus (Theorell et al., 1995; Leserman et al., 2000). Despite examples of social environment altering disease outcome via its effects on the immune response, particularly the inflammatory processes, little is known regarding the physiological mechanism underlying such actions. Oxytocin facilitates social bonding and immune function while attenuating the stress system. Thus, the health and immune promoting effects of social support may occur via an oxytocin-mediated mechanism. Recent studies have evaluated the effects of oxytocin on the immune response after injury or infection and in periods of social stress-induced immunosuppression in humans and animals. For example, men and women healed blister wounds faster when plasma oxytocin levels were elevated during a social support task in which participants had more positive interactions with their partner (Gouin et al., 2010). In rodents, daily oxytocin treatments decrease experimentally-induced inflammation and neutrophil accumulation, accelerate wound healing, decelerate atherosclerosis, and attenuate isolation- and glucocorticoid-induced delays in wound healing, while an oxytocin receptor antagonist blocks these effects (Petersson et al., 1998; Petersson et al., 2001; Detillion et al., 2004; eri et al., 2005; eri et al., 2008; Vitalo et al., 2009; Yang et al., 2010; Ahmed and Elosaily, 2011). Oxytocin treatments also alleviate dermal degeneration and reduce ileal apoptosis when coupled with social-housing in rats (eri et al., 2010). Recently, Karelina and colleagues (2011) noted that isolated mice have greater infarct size, neuroinflammation, and oxidative stress following experimental stroke than socially housed mice. However, oxytocin treatment reduces these isolation-induced effects, while treatment with an oxytocin receptor antagonist inhibits the neuroprotective effects of social housing. Thus, oxytocin also seems to have

neuroprotective effects associated with recovery from strokes. Oxytocin may modulate the immune and inflammatory response by inhibiting glucocorticoid immunosuppression. As reviewed above, glucocorticoids are released as a function of social stress (e.g., Crawley, 1984; Padgett et al., 1998b), which clearly suppresses the immune response and leads to delayed wound healing (Suh et al., 1992; Gordon et al., 1994; Hübner et al., 1996; Padgett et al., 1998a; Cole et al., 2009). Oxytocin treatment can inhibit the stress-induced rise in glucocorticoids and delay in wound healing in socially isolated hamsters (Detillion et al., 2004). Further, socially housed hamsters have delayed wound healing during treatment with an oxytocin receptor antagonist (Detillion et al., 2004). Similar oxytocin-mediating effects have been reported for other physical ailments (e.g., functional gastrointestinal disorders: Babygirija et al., 2010; Zheng et al., 2010). Together, social isolation impairs wound healing, while social housing and oxytocin attenuates these effects. This suggests stress-induced activation of the HPA axis delays wound healing and that positive social interactions may buffer against these effects via an oxytocin-mediated mechanism.

Alternatively, oxytocin may modulate the inflammatory response directly as oxytocin and functional oxytocin receptors are expressed in the thymus system (Geenen et al., 1986; Elands et al., 1990; Hansenne et al., 2005; Ndiaye et al., 2008). For example, oxytocin receptors are expressed on T lymphocyte (e.g., CD4+, CD8+, and gamma delta+), macrophages, and monocyte cells, and oxytocin treatment can also elicit a functional Ca^{2+} response in T lymphocytes (Ndiaye et al., 2008; Szeto et al., 2008). Plasma oxytocin levels are positively correlated with CD4+ cell count and modulate the relationship between social and life stress and immune function in low-income ethnic minority women with HIV (Fekete et al., 2011). Moreover, oxytocin treatment has a profound and extensive effect on the lymphoid cells and inflammatory chemicals. In healthy women, oxytocin treatment increases the phytohemagglutinin-induced peripheral blood mononuclear cells response – round nuclear cells critical in the immune response to fight infection – as well as the expression of IL-2 receptor CD25 and the CD95 activation marker on the membrane of these cells, whereas oxytocin receptor antagonist treatment inhibited the oxytocin-induced promotion of peripheral blood mononuclear cells (Macciò et al., 2010). Oxytocin can also slow down the inflammatory responses to endotoxins in healthy men, suppressing circulating inflammatory and proangiogenic cytokines (e.g., tumor necrosis factor (TNF)- α , IL-1 receptor antagonist, IL-4, and IL-6), chemokines (e.g., MIP-1 α , MIP-1 β , monocyte chemoattractant protein-1, and interferoninducible protein-10), and vascular endothelial growth factors (Clodi et al., 2008). In rats, oxytocin treatment decreases the release of IL-6 from the neurointermediate pituitary lobe, *in vitro* (Spangelo et al., 1994) and depresses the concentration of TNF- α when coupled with social-housing (Ceri et al., 2010). Thus, oxytocin may act to promote the immune response to injury and infection by directly modulating the production of cells and chemical factors (such as proinflammatory cytokines) critical to the inflammation process. Beyond the inflammatory effects, daily oxytocin treatments elevate circulating insulin-like growth factor-1 concentrations in rats (Petersson et al., 1998) – which stimulate mitotic activity and cell proliferation (Cohick and Clemmons, 1993), inhibit apoptosis (Rodriguez-Tarduchy et al., 1992), and accelerate wound healing (Suh et al., 1992). Thus, oxytocin may also promote immunological function and response to injury via activation of growth factors. To this end, oxytocin may affect the development and progression of ovarian carcinoma cells. Oxytocin receptors are expressed in a large majority of human ovarian carcinoma tissue, and cancer cell proliferation, migration, and invasion are inhibited by oxytocin treatment *in vitro* and *in vivo* in mice (Morita et al., 2004). Whittington et al. (2007) noted that oxytocin concentrations were increased in benign and decreased in malignant prostate disease, and changes in oxytocin concentrations in the prostate may facilitate cell proliferation. Along with the fact that oxytocin can inhibit proangiogenic molecules such as vascular endothelial growth factor in

healthy men (Clodi et al., 2008), there may be a biological role for oxytocin in cancer progression (further discussed in Cassoni et al., 2004).

Summary

Social stress can be a catalyst for physiological and immunological dysfunction that can embellish into detriments in mental and physical health. The negative effects of social stress on mental and physical health are often contemporaneous and not necessarily autonomous. For example, patients with cancer and other potentially terminal diseases are at risk for developing depression (Carpenter et al., 2010). In addition, participants with higher depression scores have slower wound healing (Bosch et al., 2007). Although a number of non-biological factors (e.g., perspective of poor health or one dying) may contribute, the physiological changes of a primary condition could compound and potentiate comorbidity of another mental or physical pathology.

Adult social relationships are vital to the fitness and well-being of humans and essentially all mammals, and the impact of social interaction on mental and physical health can be concomitant. Social support originating from intimate social relationships can improve the recovery of physical diseases and disorders by improving the psychological state of the patient and alter the physiological pathways that modulate mental and physical health. The communication between the central nervous system and social environment occurs via a complex network of bidirectional signals linking the nervous, endocrine, and immune systems. Furthermore, stress has an intricate, reciprocal relationship to social bonds. Disruption or absence of adult social bonds in humans and socially monogamous mammals evokes a significant physiological, immunological, psychological, and behavioral stress response, while preservation of the pair bond buffers against the negative consequences of a stressful environment (e.g., humans: Cohen and Wills, 1985; Kirschbaum et al., 1995; Powers et al., 2006; Diamond et al., 2008; marmosets: Smith et al., 1998; Gerber et al., 2002; Rukstalis and French, 2005; titi monkeys: Mendoza and Mason, 1986a; prairie voles: DeVries et al., 2003; Smith and Wang, 2011; guinea pigs: Sachser et al., 1998). This suggests that the conservation of social bonds may occur, in part, from the psychological distress and physical health risks associated with bond disruption or loss and the anxiolytic benefits of social interactions. As positive social contact is vital to promote relationships (reviewed in Dunbar, 2010), the neuroendocrine systems that regulate these bond-promoting behavior such as the oxytocin system (e.g., Williams et al., 1992; Winslow et al., 1993; Williams et al., 1994; Insel and Hulihan, 1995; Cho et al., 1999; Ross et al., 2009; Smith et al., 2010; Snowdon et al., 2010) could have been adopted in reducing stress but altering HPA axis activity or interacting pathways. The action of the oxytocin system promoted by physical contact and other social cues as well as the sense of security associated with positive social relationships provide various mechanisms whereby social interaction can provide a buffer against stress, ultimately improving health and well-being. With these effects, it is not surprising oxytocin has been suggested as a treatment for several stress-related psychological disorders such as post-traumatic stress disorder, social anxiety disorder, schizophrenia, and borderline personality disorder (Olff et al., 2010; Meyer-Lindenberg et al., 2011).

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