INVITED REVIEW

Oxytocin and hypothalamo-pituitary-adrenal axis

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ABSTRACT: Upon exposure to different types of stressors, neuroendocrine and behavioral responses that include the activation of the hypothalamus-pituitary-adrenal (HPA) axis are given to allow the individuals to cope with stress conditions. It was proven that oxytocin, a nonapeptide released from the posterior pituitary, has behavioral and stress-attenuating effects by dampening HPA activity. On the other hand, the neuropeptide was also shown to exert anti-inflammatory effects through the modulation of immune and inflammatory processes in several experimental models of tissue injury. The findings of recent studies suggest that the anti-inflammatory effect of oxytocin depends on its role on HPA axis activity and subsequent release of cortisol. Thus, oxytocin seems to restrain the activity within the HPA-axis, which becomes overactive during many inflammatory processes.

KEY WORDS: stress, oxidative stress, HPA axis, oxytocin

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INTRODUCTION

When a threat to homeostasis is perceived, hypothalamus-pituitary-adrenal (HPA) axis is activated as an important regulatory mechanism of the stress response. HPA axis activity is initiated by the secretion of corticotropin-releasing hormone from the hypothalamus, activating the secretion of adrenocorticotropic hormone from the pituitary, which then stimulates the secretion of glucocorticoids from the adrenal glands. On the other hand, oxytocin has been generally described as another important regulator of neuroendocrine and behavioral stress-coping strategies. In addition to several animal and human studies suggesting that oxytocin reduces the stress response by dampening HPA activity, recent studies reviewed in this chapter imply that the anti-inflammatory effects of oxytocin may also be operating through the inhibition of HPA activity.

Stress and HPA axis

Exposure to physiological or psychological stress causes a wide range of autonomic, endocrine, and behavioral responses, which are mostly designed to re-establish homeostasis and allow the individual to cope with stress conditions. When an individual perceives a threat to homeostasis, an important regulatory mechanism of the stress response is the activation of the HPA axis, used by most mammals to maintain homeostasis after various types of challenges. However, some individuals may display reduced neuroendocrine and behavioral responses to stress, while excessive and/or long-term activation of stress pathways may disturb these physiological and behavioral functions (41).

Regulation of HPA axis

HPA axis activity is governed by the secretion of corticotropin-releasing hormone (CRH) from the hypothalamus, which activates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary. ACTH, in turn, stimulates the secretion of glucocorticoids from the adrenal glands. Glucocorticoids interact with the corticosteroid receptors, which are present in almost every tissue in the body. Cortisol affects a multitude of systems in the body, including the HPA axis itself (Fig. 1), the cardiovascular system, the immune system, metabolism, and cell growth, and it also has an impact on behavior.

Sensory information is processed in the basolateral amygdala and relayed to neurons in the central nucleus. Descending pathways from the central nucleus of amygdala, called the bed nucleus of the stria terminalis, activate the HPA axis and the stress response. Basal and stress-induced activity of the HPA axis is controlled by glucocorticoid negative feedback (21). When circulating

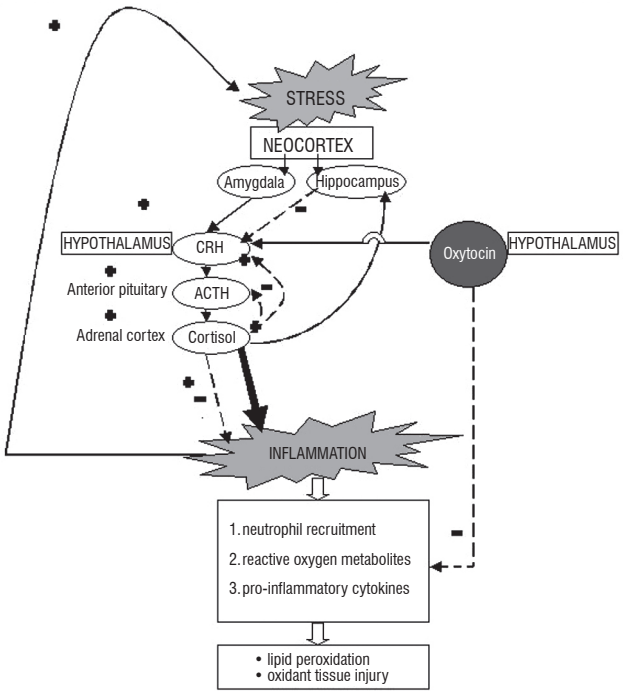

FIGURE 1. The relationship between the HPA axis and oxytocin (CRH: Corticotropin releasing hormone, ACTH: adrenocorticotropic hormone).

cortisol levels get too high, hippocampus, which contains numerous glucocorticoid receptors, inhibits CRH release and participates in the feedback regulation of the HPA axis (Fig. 1). However, continuous exposure to cortisol, such as during periods of chronic stress, can cause hippocampal neurons to degenerate, setting off a vicious cycle, in which the stress response becomes more pronounced, leading to even greater cortisol release and more hippocampal damage. In accordance with that, human brain imaging studies have shown a decrease in the volume of the hippocampus in some people suffering from post-traumatic stress disorder (3). Moreover, experimental studies have shown that adult rats with reduced anxiety express more glucocorticoid receptors in their hippocampus and less CRH in their hypothalamus, when they have received a lot of maternal care as pups. Thus, having more glucocorticoid receptors prepare the animal to respond to stressors as adults (3). It was demonstrated that the maternal influence could be replaced by increasing the tactile stimulation of the pups. Tactile stimulation activates the ascending serotonergic inputs to the hippocampus, and the serotonin triggers a long-lasting increase in the expression of the glucucorticoid receptor gene. Tactile stimulation, on the other hand, is well known to produce elevations in oxytocin, an effective regulator of the HPA axis (13).

Oxytocin and stress

Oxytocin (OT), which displays a potent anti-stress effect in several species, is a nonapeptide synthetized in the magnocellular and the parvocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus and released from the posterior pituitary axon terminals directly into the bloodstream (23). Apart from its presence in the hypothalamic neurons, OT is found in several other brain regions, including bed nucleus of the striae terminalis, central and medial nuclei of the amygdala, septum and hippocampus (1, 38), suggesting its role in the regulation of stress response.

Oxytocin has a major role in stimulating contractions of the myometrium during parturition and in driving the milk ejection reflex during suckling (37). Studies have shown that suckling in the post-partum period is associated with decreased HPA axis activity (6) and that lactating rats demonstrate blunted adrenocorticotropic hormone (ACTH) and cortisol secretion to various forms of stressors (45). OT is also secreted in response to hyperosmotic stimuli, and causes natriuresis in the rat via the stimulation of atrial natriuretic peptide secretion (14). In addition, OT can act like vasopressin via the V1b receptors on corticotrophs and may further stimulate the action of CRH on ACTH secretion (25). OT has a role in social behaviors in many species, and may have similar effects in humans. A number of animal studies suggest that OT is involved in the stress response, in particular, in reducing stress by dampening HPA activity (27). Chronic treatment of female rats with oxytocin results in a transient increase in corticosterone, followed by sustained suppression of the HPA axis (32). Moreover, OT injections have been associated with decreased cortisol levels in female rats (43), anxiolytic-like effects and sedation in male rats (44), and reduced reactivity to painful stimuli (24). In contrast to the inhibitory effects of OT on the HPA axis, treatment of rodents with a selective OT antagonist increases basal and stress-induced corticosterone response (29) and reverses the effects of pair bonding on HPA axis activity (7). However, the behavioral effects of OT are thought to reflect release from centrally-projecting oxytocinergic neurons, different from those that project to the pituitary gland (16).

Anti-inflammatory effects of oxytocin via the HPA axis

OT has anti-inflammatory effects on carrageenan-induced hyperalgesia and neutrophil accumulation in the hindpaw, through the modulation of immune and inflammatory processes, including the inhibition of the release of some interleukins (20). OT was proven to possess antisecretory and antiulcer effects (23), facilitate wound healing and increase the survival of ischemic skin flaps in rats (33). In accordance with its anti-inflammatory effects, analgesic and thermoregulatory effects of OT have also been reported (35). Recently, we have shown its anti-inflammatory effects in colonic inflammation (19), burn injury (18) and renal damage (5, 42). We have also shown that OT protects against hepatic injury in sepsis and hepatic ischemia-reperfusion models in the rat (8, 17).

Oxytocin might act through many alternative mechanisms via various mediators to ameliorate inflammatory processes and organ function (Fig. 1). It was previously reported that during the acute phase response of inflammation, the activation of the HPA axis results in an increase in glucocorticoids, which attenuate the inflammatory reaction (12), while adrenalectomy or OT treatment facilitated wound healing, through a mechanism that involves OT-induced suppression of the HPA axis (7). OT has been shown to affect several mediators involved in the pathogenesis of inflammation, by decreasing the release of interleukins and influencing the coagulation and the fibrinolytic system (39). Moreover, OT receptor gene contains response elements for acute phase reactants and interleukins, including IL-6,

prostacylin, nitric oxide, IGF-I and growth hormone (20). OT was shown to increase corticosterone levels acutely in rats (11), and therefore it is likely that the anti-inflammatory action of OT may be caused by a rise in corticosterone, which is capable of inhibiting neutrophil extravasation in response to different stimuli (31).

It is well known that oxidant injury is initiated by free radicals and reactive oxygen molecules generated by activated neutrophils, monocytes and mesangial cells during inflammatory processes (2). In many inflammatory processes, important components of pathological processes are linked to the ability of neutrophil leukocytes to release a complex assortment of agents that can destroy normal cells and dissolve connective tissue. Observations suggest that reactive oxygen metabolites (ROM) play a role in the recruitment of neutrophils into the injured tissue, but activated neutrophils are also a potential source of ROM (22). In the presence of neutrophil-derived myeloperoxidase (MPO), which is an essential enzyme for normal neutrophil function, ROM can generate hypocholorus acid and initiate the deactivation of antiproteases and activation of latent proteases, which destroy normal cells and dissolve connective tissue (40) and lead to tissue damage. In the studies we have performed (Table 1), elevated MPO activity in the studied tissues indicates that inflammatory processes involved the contribution of neutrophil infiltration. Since OT administration was found to be effective in all the injured tissues with a concomitant reduction in tissue neutrophil infiltration, as assessed by reduced MPO activity, it seems likely that the protection accomplished by OT treatment in the inflamed tissues may be attributed to its direct effect on leukocytes, suggesting that OT ameliorates oxidative organ damage via a neutrophil-dependent mechanism. On the other hand, glucocorticoids are capable of inhibiting neutrophil recruitment by acting at the rolling, adhesion, extravasation and migration of the neutrophils, by downregulating the expression of intercellular adhesion molecules (15) and have been proposed as therapeutic tools in protecting against systemic inflammation and were shown to reduce the incidence of neutrophil-mediated tissue injury and organ dysfunction (36). Taken together, the data of aforementioned studies suggest that the inhibitory effect of OT on tissue neutrophil accumulation may involve the action of endogeneous glucocorticoids, the most potent endogenous inhibitors of inflammation.

Several studies demonstrated that inflammatory processes are associated with ROM-induced lipid peroxidation, which is an autocatalytic mechanism leading to oxidative destruction of cellular membranes, and their destruction can lead to the production of toxic, reactive metabolites and cell death (9). Membrane peroxidation leads to changes in membrane fluidity and permeability and also to enhanced rates of protein degradation, eventually leading to cell lysis. In our previous studies, we have shown that malondialdehyde (MDA), an end product of lipid peroxidation, is formed in increased concentrations in the injured tissues (Table 1). OT, however, suppressed this production, indicating that OT reduces lipid peroxidation, and thereby supports the maintenance of cellular integrity by limiting the damaging effects of HPA overactivity. In accordance with this discussion, it was proposed that CRH, when applied in lower concentrations, might act directly on the neurons to protect them from various insults. However, in chronic forms of neuronal injury, CRH may reach a threshold concentration that causes it to become directly neurotoxic (30), by causing the release of toxic substances from non-neuronal cells, such as inflammatory mediators from microglial cells. Thus, it was suggested that the beneficial versus adverse effects of CRH to neurons seem to be dependent on its concentration and type of injury. Similarly, it is also expected in the peripheral tissues that the activation of the HPA axis may be either protective or deleterious depending on the concentrations of the HPA-axis linked mediators. It is possible to say that anti-inflammatory

TABLE 1. The anti-inflammatory effects of oxytocin in various models of inflammation.

Experimental inflammatory models	observed tissues	treatment	tissue MDA level	tissue GSH level	tissue MPO activity	serum TNF-α level	Reference
pyelonephritis	kidney	saline	↑↑↑	↓↓↓	↑↑↑	↑↑↑	5
		oxytocin	↓	↑	↓↓	↓↓↓	
burn	stomach	saline	↑↑↑	N/A	↑↑↑	↑↑↑	18, 19
		oxytocin	↓↓↓		↓↓	↓↓↓	
ischemia-reperfusion	liver	saline	↑↑↑	ns	↑↑	↑↑↑	8
		oxytocin	↓↓↓	ns	↓↓	↓↓↓	
ischemia-reperfusion	kidney	saline	↑↑↑	↓↓↓	↑↑↑	↑↑↑	42
		oxytocin	↓↓↓	↑↑	↓↓	↓↓↓	
sepsis	colon, liver, uterus	saline	↑↑ - ↑↑↑	↓ - ↓↓	↑ - ↑↑↑	↑↑↑	17
		oxytocin	↓ - ↓↓	↑	↓ - ↓↓↓	↓↓↓	

↑, ↑↑, ↑↑↑ ($p<0.05$, $p<0.01$, $p<0.001$, respectively): increased significantly with respect to control groups.
↓, ↓↓, ↓↓↓ ($p<0.05$, $p<0.01$, $p<0.001$, respectively): deccreased significantly with respect to control groups.
↑, ↑↑ ($p<0.05$, $p<0.01$, respectively): increased significantly with respect to saline-treated groups.
↓, ↓↓, ↓↓↓ ($p<0.05$, $p<0.01$, respectively): decreased significantly with respect to saline-treated groups.
(MDA: malondialdehyde, MPO: myeloperoxidase activity, GSH: glutathione, TNF-α: tumor necrosis factor alpha, ns: not significant, N/A: not applicable.)

effect of OT partially depends on its role on HPA axis activity and cortisol levels, because OT, when administered in high doses, may increase corticosterone levels acutely in rats (10). A single injection of OT was shown to cause a transient increase in ACTH and corticosterone, while a sustained decrease in corticosterone levels was observed in the long-term (32). Thus, OT seems to stimulate as well as to inhibit the activity within the HPA-axis within a short- and a long-term perspective, respectively. On the other hand, glucocorticoid receptor mRNA levels in the hippocampus were shown to change in response to the oxytocin treatment (34).

Glutathione (GSH), which provides a cellular defense against oxidative injury, is frequently used as a measure of tissue antioxidant status. Therefore, presence of reduced GSH levels shown in most of the studied tissues affected by different models of inflammation may be considered as a sign of diminished antioxidant pool in these tissues (Table 1). On the other hand, oxytocin administration prevented the depletion of tissue GSH contents of inflamed tissues. These results suggest that OT may have a direct effect on either the consumption or the production of this intracellular antioxidant in many tissues, but it does not exclude the possibility that OT may also be effective in stimulating the activity of other antioxidants. In accordance with our results, it was shown in brain membranes that OT displayed antioxidant properties in aqueous medium, scavenging free peroxyl radicals, preventing LDL oxidation and inhibiting lipid peroxidation (26).

In accordance with the reversal of inflammation-induced alterations in tissue MPO activity, MDA and GSH levels, serum TNF-α levels were also depressed in OT-treated animals with different inflammations (Table 1). In contrast to inhibitory action of OT on TNF-α release observed *in vivo*, it was shown in fetal membranes that both expression of tissue mRNA for TNF-α and TNF-α release in culture medium were significantly increased by OT (46). It is accepted that the HPA-axis response after an endotoxin challenge is mainly due to released cytokines, namely interleukin-1, interleukin-6 and TNF-α from stimulated peripheral immune cells, which in turn stimulate different levels of the HPA axis. However, the resulting increase in adrenal glucocorticoids has well-documented inhibitory effects on the inflammatory process and on inflammatory cytokine release (4). The reversal of oxidative injury concomitant with inhibited TNF-α response by OT treatment suggests that the mechanism of the protective effect of OT involves the inhibition of inflammatory cell infiltration and the release of TNF-α through the suppression of HPA activity.

Apart from the modulatory role of oxytocin in a wide variety of social behaviors, including maternal care and aggression, pair-bonding, sexual behavior, social memory and support, it is an important regulator of the stress response via its inhibitory effects on HPA responses (23, 28, 38, 45). Moreover, during many inflammatory events, OT seems to restrain the activity within the HPA-axis, which becomes overactive by activated immune cells and released pro-inflammatory cytokines.

Oksitosin ve hipotalamus-hipofiz-adrenal bez ekseni

ÖZET: Strese yol açan farklı uyaranlarla karşılaşıldığında, bireylerin bu stres koşulları ile baş edebilmelerini sağlamak üzere birçok mekanizma ile birlikte, hipotalamus-hipofiz-adrenal bez ekseni (HPA)'nin uyarılmasını da içeren nöroendokrin ve davranış yanıtları ortaya çıkar. Yapılan çalışmalar, arka hipofizden serbestlenen dokuz amino asitli oksitosinin, HPA aktivitesini baskılayarak davranışsal ve stres-azaltıcı etkileri olduğunu göstermiştir. Diğer taraftan, bu nöropeptidin çeşitli deneysel doku hasarı modellerinde immün ve inflamatuvar süreçleri düzenleyerek anti-inflamatuvar etki gösterdiği de ortaya konmuştur. Yeni yapılan çalışmaların sonuçları, oksitosinin HPA ekseni aktivasyonuna ve sonucunda kortizol serbestlenmesine olan etkileri ile anti-inflamatuvar etki gösterebileceğini düşündürmektedir. Sonuç olarak oksitosin, birçok inflamatuvar olayda aşırı uyarılmış olan HPA ekseninin etkinliğini sınırlandırmak yoluyla etki göstermektedir.

ANAHTAR KELİMELER: stres, oksidan stres, HPA ekseni, oksitosin

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