

Anti-stress Effect of Hypothalamic Oxytocin, Importance of Somatosensory Stimulation and Social Buffering

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ABSTRACT

A growing body of evidence suggests that stress stimuli, both acute and chronic, promote different physiological mechanisms and neuroendocrine responses. Oxytocin (OXT) is mainly synthesized in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus. Central OXT has an anxiolytic effect and attenuates the hypothalamic–pituitary–adrenal (HPA) axis in response to stress. Anti-stress effect of OXT has been explained by its inhibitory effect on corticotropin releasing factor (CRF) expression at the PVN via GABA_A receptors. Repeated experience with the same stressor produces habituation, or diminution of behavioral responses and HPA axis responses. Up-regulated OXT expression in the PVN is involved in mediating habituation in response to chronic homotypic stress in rats. In contrast to chronic homotypic stress, no habituation is observed when rats are singly housed and received different types of stressors for 7 days (chronic heterotypic stress). Increased CRF expression and reduced OXT expression at the PVN are observed following chronic heterotypic stress in singly housed rats. Thus, it is conceivable that stress responses to chronic heterotypic stress would be diminished if endogenous OXT expression is upregulated. Various manual therapies such as massage,

acupuncture and transcutaneous electrical nerve stimulation (TENS) involve the stimulation of somatosensory neurons. OXT system is activated by manual therapies. TENS increases OXT expression and decreases CRF expression at the PVN following chronic heterotypic stress in singly housed rats. OXT has been implicated in a number of social behaviors, including maternal care, affiliation and social attachment. Social attachment is known to stimulate OXT release in the hypothalamus in rats. A recent study demonstrates an increased OXT expression following chronic heterotypic stress when rats are pair-housed. Somatosensory stimulation is a promising treatment for stress-associated diseases. A social interaction is also important to adapt to our daily life stress.

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Key words: Acupuncture; CRF; Hypothalamus; HPA axis; Social interaction

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EDITORIAL

1. Functional GI disorders and stress

1-1. GI dysmotility following acute stress: Functional gastrointestinal (GI) disorders include functional dyspepsia (FD) and irritable bowel syndrome (IBS). Functional GI disorders are common in the general population, with a reported prevalence of 25-40%. The motor dysfunction of colon and visceral hypersensitivity are considered especially important factors of functional GI disorders^[1,2]. Stress is highly associated with functional GI disorders and GI

symptoms may develop when we fail to adapt to various stressors in our daily life.

Corticotropin releasing factor (CRF) neurons are located in the PVN of the hypothalamus, amygdala and locus coeruleus complex^[3]. Acute restraint stress stimulates CRF release, resulting in activation of the hypothalamic–pituitary–adrenal (HPA) axis. Released CRF also influences GI motility via projecting to the autonomic preganglionic neurons at the brain stem^[4]. CRF-mediated motor responses differ between the stomach and colon. Gastric emptying of solid and liquid meals is delayed by acute restraint stress in rodents^[5]. In contrast, acute restraint stress accelerates colonic transit in rats^[6] and mice^[7].

There are two distinct CRF receptors, subtype 1 (CRF type₁) and subtype 2 (CRF type₂). The different motor patterns between the upper and lower gut are mediated via different CRF receptors. Delayed gastric emptying induced by acute restraint stress is mediated via central CRF₂ receptors^[5]. In contrast, accelerated colonic transit induced by acute restraint stress is mediated via central CRF₁ receptors in rats^[6].

Acute restraint stress stimulates central CRF₂ receptors and sympathetic pathway, resulting in delayed gastric emptying^[5] (Figure 1), while acute restraint stress stimulates central CRF₁ receptors and parasympathetic pathways (vagal nerve and pelvic nerve), resulting in acceleration of colonic transit in rats^[6] (Figure 1).

As CRF₁ receptors are expressed in the myenteric plexus of the rat colon, it has been suggested that stress-induced acceleration of colonic transit is mediated via peripheral CRF receptors^[8], in addition to the central CRF receptors. However, a clinical trial demonstrated that peripheral administration of a selective CRF₁ receptor antagonist (pexacerfont) failed to affect colonic transit and bowel function in IBS patients^[9], indicating that peripheral CRF₁ receptors are not involved in mediating colonic dysmotility in IBS patients. Although the motor responses to acute restraint stress differ between upper and lower GI tract, it should be noted that both responses are mediated via the same neuropeptide of the CNS, which is CRF.

1-2. Anti-stress effect off OXT following acute stress:

Oxytocin (OXT) is mainly produced in neurons originating in the paraventricular nucleus (PVN) and supraoptic nucleus (SON) of the hypothalamus. Besides female reproductive functions, OXT is also known for its anti-stress and anti-anxiety effects^[10]. OXT attenuates HPA axis in response to stress^[10]. Delayed gastric emptying and accelerated colonic transit induced by acute restraint stress are abolished by intracerebroventricular (icv)-injection of OXT in rats^[11,12].

Anti-stress and anti-anxiety effects of OXT are mediated by its inhibitory effect on CRF mRNA expression^[13]. The inhibitory effect of OXT on CRF expression may not have a direct effect on CRF neurons, because the majority of neuronal responses to OXT are excitatory. GABAergic neurons are located in the immediate surroundings of the PVN (peri-PVN). These GABA-projecting neurons into the PVN have been shown to inhibit CRF synthesis via GABA_A receptors^[14]. A recent study demonstrated that the inhibitory effect of OXT on CRF mRNA expression is mediated by GABA_A receptors at the PVN^[15] (Figure 2). In the central amygdala, others also showed that OXT enhances GABAergic transmission through an increased frequency of the inhibitory postsynaptic currents^[14].

Central-injection of OXT, but not peripheral-injection of OXT, significantly improves delayed gastric emptying induced by acute restraint stress in mice^[16] and rats^[11]. Similarly, water avoidance stress-induced acceleration of colonic motility is attenuated by central, but not peripheral, administration of OXT^[17]. Microdialysis

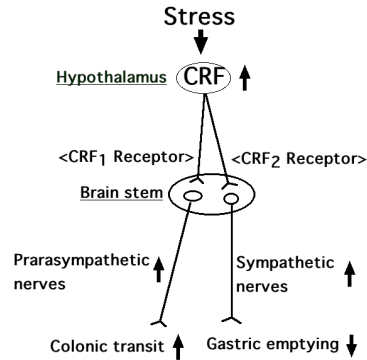


Figure 1 Mechanism of delayed gastric emptying and accelerated colonic transit following acute stress. Delayed gastric emptying induced by acute stress is mediated via central CRF₂ receptors and sympathetic pathways. In contrast, accelerated colonic transit induced by acute stress is mediated via central CRF₁ receptors and parasympathetic pathways. Released Ach stimulates colonic motility, while released CA inhibits gastric motility.

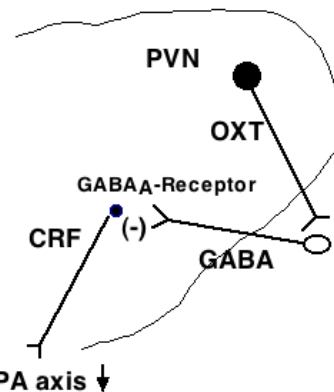


Figure 2 OXT inhibits CRF expression via GABA_A receptors at the PVN.

study showed a significant increase of central OXT, but not peripheral OXT, in response to chronic stress^[18]. Thus, central OXT plays a predominant role in regulating stress-induced GI dysmotility. Although OXT and its receptors are expressed on the smooth muscle cells, enteric neurons and intestinal epithelium of the GI tract^[19], peripheral OXT may not have a major role in attenuating stress responses.

1-3. Habituation of GI motility following chronic homotypic stress:

Repeated experience with the same stressor produces habituation, or diminution of behavioral responses and HPA axis responses. Delayed gastric emptying and accelerated colonic transit observed in acute stress are restored to normal levels following repeated stress loading (chronic homotypic stress) for 5 days in rats^[20] and mice^[16]. Restored gastric emptying following chronic homotypic stress is reversed by icv-injection of OXT antagonists^[11]. OXT knockout (KO) mice fails to restore gastric emptying^[21] and colonic transit^[7] following chronic homotypic stress. These suggest that central OXT is involved in mediating the adaptation mechanism in response to chronic homotypic stress. Up-regulated OXT expression at the PVN inhibits CRF expression, resulting in reduced HPA axis activity and restoration of GI motility following chronic homotypic stress^[11] (Figure 3b).

The mechanism of upregulated OXT expression at the hypothalamus following chronic homotypic stress remains unclear. It has been shown that noradrenergic and serotonergic transmission plays important roles in neuroendocrine stress responses.

Hypothalamic magnocellular neurons receive input from A₁ and A₂ noradrenergic neurons in the medulla oblongata. A variety of stressful stimuli activate medullary noradrenergic neurons, which stimulate OXT release from the PVN via alpha₁ adrenergic receptors.

Serotonergic (5-HT) neurons originating in the dorsal and median raphe nucleus project to the PVN. 5-HT is able to stimulate OXT neurons via 5-HT_{1A}, 5-HT_{2A} and 5-HT_{2c} receptors. OXT release is also regulated via histamine, glutamate, opioids and dopamine (DA)^[22]. It needs to be studied whether upregulation of OXT following chronic homotypic stress is mediated via adrenergic, serotonergic, or other receptors.

1-4. Mal-adaptation (non-habituation) following chronic heterotypic stress: In modern society, individuals encounter various types of physical, mental and social stress on a daily basis. To replicate complex stress exposure in humans, rats are loaded different types of stressors for 7 consecutive days (chronic heterotypic stress). In contrast to chronic homotypic stress, delayed gastric emptying and accelerated colonic transit are still observed following chronic heterotypic stress^[11,12].

As mentioned above, central CRF plays a dominant role in response to acute stress. However, it is not well established whether CRF is still involved in mediating responses to chronic heterotypic stress. It has been shown that vasopressin (VP) plays a role during the adaptation to chronic stress and that VP may be the principal modulator of the HPA axis in response to chronic stress. Accelerated colonic transit and delayed gastric emptying following chronic heterotypic stress are antagonized by CRF₁ receptor antagonists and CRF₂ receptor antagonists, respectively^[12]. In addition, icv-injection of VP receptor antagonists have no significant effects on GI dysmotility following chronic heterotypic stress. These suggest that central CRF receptors play a major role in mediating GI dysmotility following chronic heterotypic stress. Lower OXT expression and higher CRF expression at the PVN are observed following chronic heterotypic stress^[11]. These indicate that chronic heterotypic stress fails to adapt GI dysmotility due to hypersecretion of CRF and impaired OXT expression at the PVN (Figure 3c).

2. Anti-stress effects of somatosensory stimulation

2-1. Effects of somatosensory stimulation on GI motility: It has been demonstrated that somatic afferents from the skin and muscle are involved in the control of various autonomic functions, including GI motility in rats and humans. The spinal–supraspinal pathways responsible for somatosensory stimulation mainly comprise the posterior column pathway and spinothalamic pathway. Most peripheral thick myelinated afferent fibers activated by the

discriminative touch and sense of vibration enter the ipsilateral dorsal column-medial lemniscus tract (posterior column pathway) and emerge into the contralateral spinothalamic pathway. In contrast, the thinly myelinated or unmyelinated afferent fibers activated by pain and temperature are carried up by the contralateral spinothalamic tract to supraspinal levels (spinothalamic pathway). These impulses are further relayed to the thalamus, and ultimately sent to the primary somatosensory cortex. In addition, these impulses are also relayed to other brain areas, including the brain stem, periaqueductal gray (PAG) and hypothalamus, via collateral connections^[23] (Figure 4).

Various manual therapies, including massage, acupuncture and transcutaneous electrical nerve stimulation (TENS), involve the stimulation of somatosensory neurons. Acupuncture involves the insertion of thin needles into the skin and underlying muscle layer. Inserted acupuncture needles are often stimulated by electricity under various frequencies of 1-100 Hz (electroacupuncture; EA). In contrast to acupuncture, TENS is a non-invasive procedure, in which electrodes are placed on the skin and stimulated by electricity.

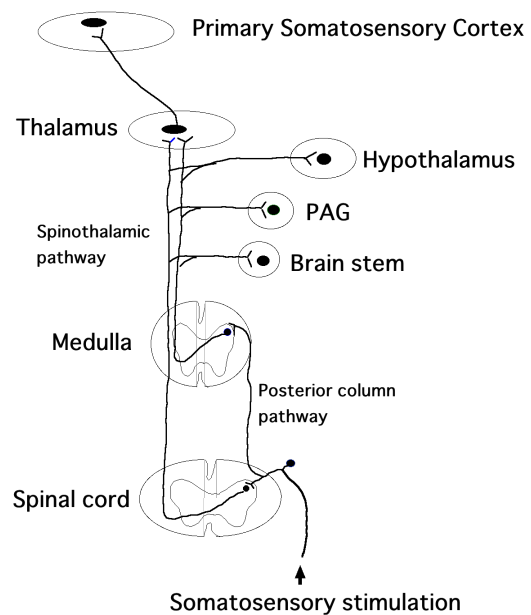


Figure 4 Somatosensory system. The spinal–supraspinal pathways responsible for somatosensory stimulation comprise the posterior column pathway and spinothalamic pathway. These impulses are further relayed to the thalamus, and ultimately sent to the primary somatosensory cortex. In addition, these impulses are relayed to other brain areas (brain stem, PAG and hypothalamus, via collateral connections.

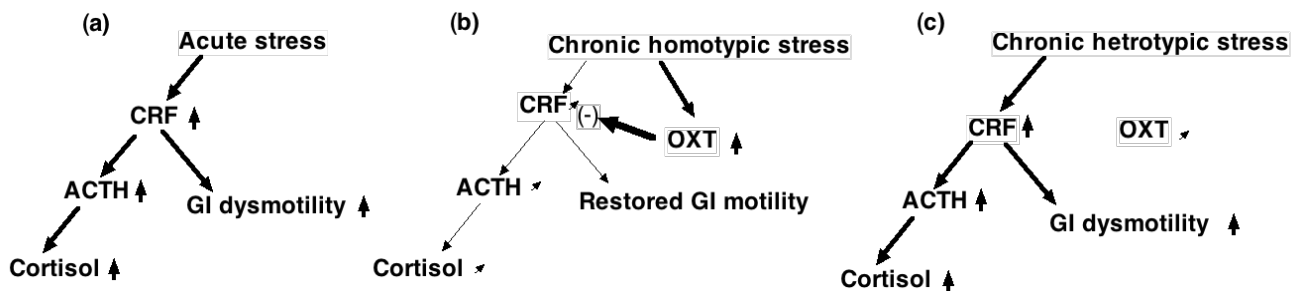


Figure 3 Interaction between CRF and OXT mediating GI motility following acute stress (a), chronic homotypic stress (b) and chronic heterotypic stress (c). Acute stress accelerates colonic transit and delays gastric emptying, and stimulates HPA axis (a). Chronic homotypic stress restores GI dysmotility, due to upregulated OXT expression (b). Chronic heterotypic stress fails to restores GI dysmotility, due to impaired OXT expression and upregulated CRF expression (c).

Acupuncture has been used for treating various GI diseases, including gastroparesis, functional dyspepsia (FD), irritable bowel syndrome (IBS), constipation and diarrhea^[24]. Recent study showed that TENS applied to the acupuncture points (transcutaneous-EA; TEA) at the hands and lower legs improves GI symptoms in patients with FD^[25]. Effects of acupuncture on GI motility is mediated via the CNS levels, not the spinal levels. Acupuncture-induced gastric relaxations were almost completely abolished by spinal transection. Acupuncture-induced gastric relaxations are reduced by spino-medullary transection, but not by ponto-medullary transection, suggesting that the reflex center of acupuncture-induced gastric relaxations is located in the medulla^[26]. Acupuncture regulates colonic motility and transit in rats via stimulating autonomic neurons in rats^[27]. These suggest that acupuncture alters GI motility via the pathways of somatosensory - spinal cord - autonomic neurons. Finally, released acetylcholine (Ach), catecholamine (CA), or other neurotransmitters from the enteric nervous system (ENS) regulates GI motility^[26,27]. Thus, it is unlikely that acupuncture primarily stimulates ENS.

2-2. Anti-stress effect of TENS and EA: Animal studies demonstrated that TENS and EA improve various stress-induced physiological responses. GI dysmotility (delayed gastric emptying and accelerated colonic transit) induced by acute restraint stress was restored by EA at the lower legs in rats^[28]. EA stimulates parasympathetic activity and inhibits sympathetic activity under the acute restraint stress loading in rats^[29]. EA is shown to attenuate stress-induced defecation reduce CRF expression at the hypothalamus in the rat IBS model^[30].

2-3. Anti-stress effects of TENS are mediated via OXT: In humans, post-traumatic stress disorder (PTSD) is marked by deficits in anxiety, stress regulation and in social functioning. Traumatic stress in the normal individual results in activation of the sympatho-adrenal system causing a rise in noradrenaline/adrenaline, and activation of the HPA system resulting in elevated cortisol levels.

OXT has unique effects of decreasing background anxiety without affecting learning and memory of a specific traumatic event in rats. Increased OXT neurotransmission during traumatic events is likely to prevent the formation of aversive memories. When OXT is centrally administered prior to fear conditioning or extinction training, fear expression and facilitated fear extinction are decreased in rats^[31]. OXT may be effective in PTSD through a reduction of fear response and an increase of social functioning. Toth *et al* proposed that OXT treatment before fear extinction training is a comparable time point for psychotherapy in PTSD patients^[32].

Various types of somatosensory stimulation (massage, EA, thermal stimulation, vibration, and afferent sciatic nerve stimulation) can increase OXT levels in plasma and cerebrospinal fluid in anesthetized rats^[33]. These raise the possibility that TENS may act on OXT neurons at the hypothalamus. GI dysmotility induced by chronic heterotypic stress is significantly improved by TENS in rats, which is abolished by icv-injection of OXT antagonists⁺. TENS increases the number of OXT-immunopositive cells and decreased CRF-immunopositive cells at the PVN following chronic heterotypic stress^[34]. These suggest that TENS activates hypothalamic OXT neurons via the spinothalamic pathway (Figure 5). Activated OXT neurons inhibit CRF expression, resulting in the attenuation of stress responses of GI tract.

Clinical trials demonstrated that acupuncture is effective for treating the patients with PTSD. People diagnosed with PTSD were randomized to either an empirically developed acupuncture treatment or a CBT group. Compared with CBT, acupuncture provided significant effects on PTSD^[35].

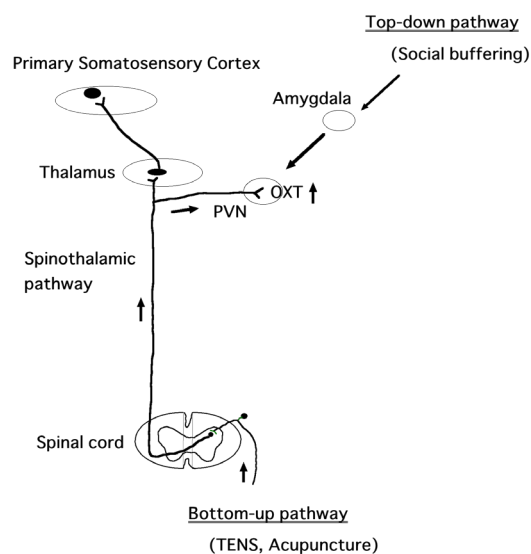


Figure 5 Top down pathway and bottom up pathway mediating up-regulation of hypothalamic OXT expression.

3. Anti-stress effects of social buffering

3-1 Anti-stress effects of social buffering following chronic heterotypic stress:

Social activity is related to beneficial effects on the cardiovascular, endocrine, and immune systems. Social connectedness may have stress-buffering effects. It is important for us to feel connected, to be trusted and loved. Feeling connected to others increases psychological and physical well-being and decreases the risk of depression and physical ailments. People with a higher quality of social relationships show a lower risk of death, while social isolation has been shown as a major risk factor for mortality. Social activities and psychological coping styles reduce the deleterious effects of stress and thus reduce the risk of disease in a non-specific way^[36,37]. Unfortunately, our society is becoming increasingly isolated and distrustful. It seems that technological, economical, and social changes have developed less trustworthiness among us.

OXT plays an important role in the ability to form social attachments including parental care, pair bonding and social memory. In humans, intranasal administration of OXT (OXT spray) increases trusting behavior^[38]. The social interaction of daily life as well as a positive environment continuously activates the system of OXT release in both males and females^[39]. Social attachment (social buffering) has been shown to stimulate OXT release in the hypothalamus in rodents^[10].

GI dysmotility following chronic heterotypic stress observed in singly-housed rats is restored, when rats are housed by pair. Paired housing decreased CRF mRNA and increased OXT mRNA expression at the PVN following chronic heterotypic stress^[40,41]. These suggest that activation of OXT signaling via social interactions can ameliorate the effects of stress on GI motility.

Amygdala is stimulated by emotional arousal, such as affective words^[42]. Amygdala is a source of efferent projections to the ventromedial hypothalamic nucleus. Outputs of the MeA to the basal forebrain and hypothalamus orchestrate the behavioral, autonomic, and neuroendocrine responses to conspecifics. Received prosocial or trust behaviors may activate efferent output from the amygdala to OXTergic systems.

Dopaminergic (DAergic) fibers regulate OXT release from the

PVN^[43]. As there are no direct projections from the MeA to the PVN^[44], it is likely that DAergic neurons are involved in relaying between MeA and PVN-OXT neurons. D₂ receptors in the nucleus accumbens are important for the mediation of social attachments in female voles^[45]. Based on these observations, it is likely that social buffering may activate the hypothalamic OXT neurons via the MeA - DAergic pathways and D₂ receptors (Figure 5).

It is emphasized that a positive social interaction, which upregulates hypothalamic OXT expression, is an important factor to overcome daily life stress and reduce GI symptoms. Studies of humans and other social animals showed widespread evidence of the beneficial effects of prosocial and altruistic behavior. Numerous studies reveal protective effects of volunteering on mental and physical health. Both consistency of volunteering over time and diversity of participation are significantly related to well-being and self-reported health. Participation in clubs and volunteer activities had a significant protective effect on mortality. Piliavin insisted that *"One does well by doing good"*^[46].

A positive social interaction is bidirectional, involving both giving and receiving empathy. A recent study showed that affiliative behavior toward others attenuates stress responses of GI tract via up-regulating hypothalamic OXT expression^[41]. This suggests that giving affection and empathy to others may be a key in upregulating hypothalamic OXT expression. As OXT is linked to health promoting cardiovascular, analgesic, and anti-stress effects, upregulated OXT expression would help to maintain our mental and physical health.

"If you want others to be happy, practice compassion. If you want to be happy, practice compassion." (Dalai Lama). Buddhist traditions have emphasized the importance of cultivating connection and love toward others through techniques such as loving-kindness meditation (LKM). A randomized clinical research has demonstrated that the practice of LKM decreased chronic low back pain, psychological distress, and anger^[47]. Thus, performance of religious thoughts provided the evidence that cultivating connection and social interaction are key factors to maintain our well-being.

Intranasal OXT administration reduces behavioral and endocrine responses to social stress, mediates social buffering, attenuates the hyperactivity of amygdala to fearful stimuli and improves social cognition and empathy^[48]. Thus, a pharmacological intervention in the OXT system can be a target for novel therapeutic approaches.

However, we cannot exclude the possibility that desensitization of OXT receptors and/or downregulation of endogenous OXT synthesis may develop when OXT is administered daily. A combination of intranasal OXT administration with TENS or social interaction might provide new insights for a better treatment of GI dysmotility and mental disorders associated with stress.

In conclusion, it is proposed that TENS/acupuncture may promote anti-stress effects via stimulating somatosensory pathway (bottom-up pathway). In contrast, social buffering may promote anti-stress effects by stimulating brain activity and throughout its network (top-down pathway). Both pathways finally activate the OXT system at the hypothalamus (Figure 5). Upregulated OXT mediates anti-stress effects. Thus, both pathways are beneficial in treating stress-associated symptoms.

During the process of maintaining the positive social interaction, both of giving and receiving empathy, OXT system is upregulated in our brain. Especially, thinking about helpless people and giving sympathy to them may upregulate hypothalamic OXT expression, which promotes mental and physical health on the givers. It is important to reconsider Buddhist traditions of cultivating connection and compassion towards others in order to maintain our well-being.

CONFLICT OF INTERESTS

The authors have no conflicts of interest to declare.

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