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Review

Beneficial Effects of Acupuncture for Depression-A Possible Mediation of Peripheral Sensory Stimulation and Central Oxytocin Release

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Abstract

In modern society, depression is one of the most common mental disorders. It is generally thought that depression is due to the disorders of neuronal circuits and chemical balance in the brain. Patients with depression often receive treatment with selective serotonin reuptake inhibitors (SSRIs). However, recent studies suggest that the magnitude of benefit of pharmacological treatment is quite limited for these patients. Although recent studies propose acupuncture as a non-pharmacological approach to managing depression, the mechanism of its beneficial effects is not well understood. Somatosensory pathways stimulated by acupuncture relay to the central nervous system (CNS). In animal studies, acupuncture has demonstrated the potential to ameliorate neural abnormalities associated with depression. As complex daily life stress is highly associated with depression, the procedure that suppresses stress responses would be a good candidate to treat depression. Oxytocin (OXT) is a hormone produced at the hypothalamus and mediates social bonding and stress reduction. OXT inhibits stress-induced corticotropin-releasing factor (CRF) expression at the hypothalamus, resulting in anti-stress and anti-anxiety effects. Research has demonstrated

that acupuncture stimulates the release of hypothalamic OXT through somatosensory stimulation. Thus, stress-related mental disorders can be treated, at least in part, by acupuncture. It is proposed that somatosensory stimulations induced by acupuncture are a possible candidate as a non-pharmacological approach for depression.

Keywords
Corticotropin releasing factor (CRF); hypothalamus; selective serotonin reuptake inhibitor (SSRI); stress

1. Introduction

The acupuncture procedure inserts thin needles into the skin and/or underlying muscle layer. Inserted acupuncture needles are sometimes stimulated by electricity with various frequencies (electroacupuncture).

Acupuncture has been employed to treat various diseases and symptoms in the Orient for thousands of years. Numerous animal and human studies have demonstrated that somatosensory stimulation can regulate autonomic nerve functions. Stimulation of sensory neurons from the skin and muscles can subsequently influence autonomic function. Acupuncture and transcutaneous electrical nerve stimulation (TENS) stimulate somatosensory neurons.

Acupuncture has demonstrated efficacy in treating a range of conditions, including gastrointestinal (GI) diseases [1], cardiovascular diseases [2], chronic pain [3], chemotherapy-induced emesis [4], inflammation [5], and others. Previous studies demonstrated anatomical/physiological evidence of how acupuncture works.

Acupuncture modulates the activity of the autonomic nervous system, improving cardiovascular and GI symptoms [1, 2]. The beneficial effect of acupuncture for chronic pain is mediated via 5-HT in the dorsal raphe nucleus and plasma met-enkephalin [3]. The anti-emetic effect of acupuncture is mediated via central opioids [6]. A recent study showed that the anti-inflammatory effect of acupuncture is mediated via the vagal-adrenal axis and NPY adrenal chromaffin cells [7].

In the recent 20 years, fMRI has been widely used to study acupuncture's effects on brain function and its network. Acupuncture encompasses cognitive regions as well as somatosensory regions [8].

In modern society, depression is one of the most common mental disorders, promoting a significant economic burden. Unfortunately, some of these patients are resistant to usual pharmacological treatments. As a non-pharmacological approach to managing depression, acupuncture has been proposed.

According to the recently published review article [9], animal and human research supported the beneficial effect of acupuncture for depression. The pathogenesis of depression is thought to be the disorders of neuronal circuits and chemical balance in the brain. These include abnormal function/structure of the specific brain regions, neuroplasticity, reduced neurotransmitters (such as glutamate and serotonin), and increased inflammatory cytokines [9]. In animal studies, acupuncture has been shown to improve these abnormalities related to depression [9].

Oxytocin (OXT) is a hormone in social bonding and reducing stress. OXT may have an important role in mediating the anti-depressive effects of acupuncture. Previous studies suggest that

acupuncture might stimulate the release of OXT, contributing to its potential therapeutic effects [10]. As mentioned below, acute and/or chronic stress is highly associated with depression. The procedure that suppresses stress responses would be a good candidate for treating depression [10].

OXT is well known to inhibit corticotropin-releasing factor (CRF) expression induced by stress, resulting in anti-stress effects. Once acupuncture can stimulate OXT release via somatosensory stimulation [10], mental disorders induced by daily life stress could be diminished. In addition to stress, various factors have been discussed in the etiology of depression, including chronic pain, brain inflammation, abnormalities in brain circuits, and others [9]. This review article focuses on the pathophysiological role of the anti-stress effects of OXT and the mechanism of acupuncture treatment for depression.

2. Effects of Acupuncture on Autonomic Nerve Function

Studies have demonstrated that acupuncture at ST-25 (abdomen) induces a relaxation of the stomach [11], whereas acupuncture at ST-36 (leg) causes a contraction of the stomach in rats [12]. Acupuncture-induced gastric relaxation is mediated via the somatosensory neurons and sympathetic neurons. Its afferent limb is the abdominal wall's cutaneous and muscle afferent nerves. Its efferent limb is the sympathetic nerves innervating to the stomach. Gastric contraction induced by acupuncture at ST-36 is mediated via the somatosensory and vagal neurons. The reflex center of gastric relaxation and contraction is within the medulla [11, 12]. Another study showed that acupuncture at ST-36 accelerates colonic transit in rats. Its afferent limb is the cutaneous and muscle afferent nerves of the foot. Its efferent limb is the pelvic nerve innervating to the colon [13].

Information from various organs, such as cardiovascular, respiratory, and GI systems, primarily reaches the brainstem's nucleus tractus solitaries (NTS). The complex of NTS and the adjacent dorsal motor nucleus of the vagus (DMV) is named the dorsal vagal complex (DVC). DVC is important in mediating the vago-vagal reflex, which regulates GI function. In addition to receiving from the visceral organs, NTS also receives somatic afferent output from the skin and muscle of the body through the spinal cord. Thus, NTS can be activated by somatosensory stimulation induced by acupuncture.

To investigate the neural pathways mediating the gastrointestinal responses induced by acupuncture, researchers conducted c-Fos immunohistochemistry on the brainstem to obtain anatomical evidence. In response to acupuncture at ST-36, c-Fos immune-positive cells are observed at NTS and DMV's medio-caudal/caudal part. This suggests that somatic afferents activated by acupuncture at ST-36 are relayed to the media-caudal and caudal parts of NTS and stimulate the DMV neurons. In contrast, c-Fos immune-positive cells are observed at medio-caudal NTS and rostral ventrolateral medulla (RVLM) in response to acupuncture at ST-25. This indicates that somatic afferents activated by acupuncture at ST-25 are relayed to the media-caudal NTS and stimulate RVLM neurons. The RVLM neurons connect with the sympathetic preganglionic neurons of the spinal cord [14] (Figure 1).

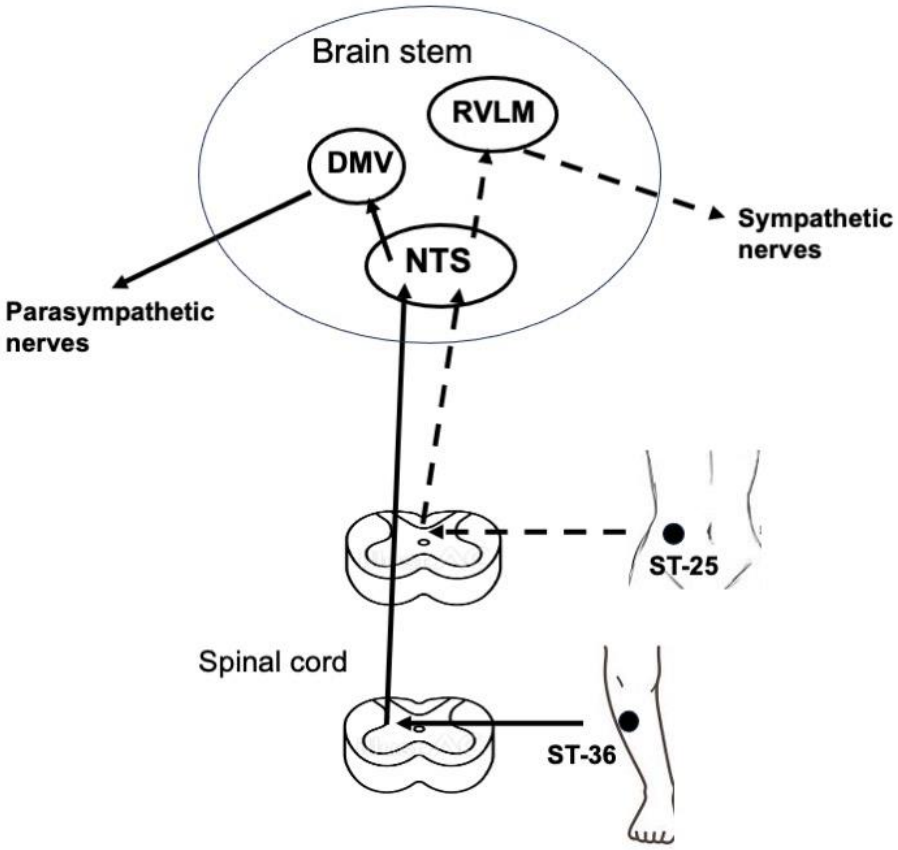

Figure 1 Possible pathways in acupuncture-mediated autonomic nervous responses. Somatic afferents activated by acupuncture at ST-36 (foot) are conveyed to the media-caudal and caudal NTS and stimulate the DMV neurons (solid lines). In contrast, somatic afferents activated by acupuncture at ST-25 (abdomen) are conveyed to the media-caudal NTS and stimulate the rostral ventrolateral medulla (RVLM) neurons (dot lines). The RVLM neurons provide a drive to the sympathetic preganglionic neurons.

The recent study also demonstrated the cite specific effects of acupuncture on autonomic nerve function. Acu-stimulation on ST-25 triggers sympathetic nerve activity, while acupuncture on ST-36 stimulates parasympathetic nerve activity [7].

Spectral analysis of heart rate variability (HRV) is well known to evaluate autonomic nervous activity. Low frequency (LF; 0.04-1.0 Hz) of HRV represents sympathetic activity, while high frequency (HF; 1.0-3 Hz) of HRV represents parasympathetic activity in rats. Following acute restraint stress loading, increased LF components and reduced HF components are observed in rats. It is suggested that acute stress increases sympathetic activity and reduces parasympathetic activity [15].

Electroacupuncture at ST-36 significantly reduced the LF component and increased the HF component following acute stress loading. Thus, electroacupuncture at ST-36 may stimulate parasympathetic activity and reduce sympathetic activity under stressful conditions [15].

3. Neural Pathway from Skin to Central Nervous System (CNS)

Somatic afferent neurons located on the skin and muscle may play an important role in controlling various autonomic nerve functions in animals and humans. The posterior column and spinothalamic

pathways are involved in mediating somatosensory pathways from the spinal cord to the CNS. Myelinated afferent fibers enter the ipsilateral dorsal column-medial lemniscus tract (posterior column pathway) and emerge into the contra-lateral spinothalamic pathway. In contrast, unmyelinated afferent fibers are carried up by the contra-lateral spinothalamic tract (spinothalamic pathway). These impulses are conveyed to the thalamus and finally sent to the primary somatosensory center of CNS. Additionally, collateral connections carry these somatosensory impulses to other areas, such as the hypothalamus, periaqueductal gray (PAG), and brain stem [16] (Figure 2).

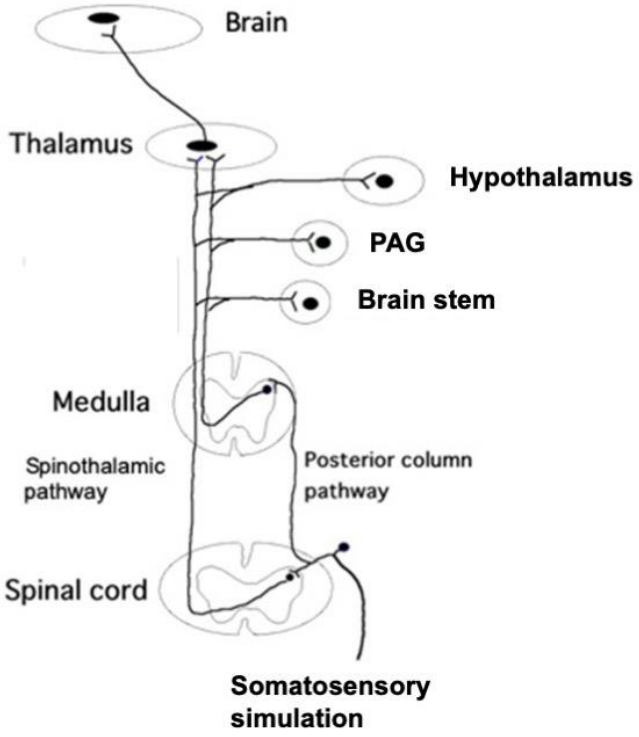

Figure 2 Relay from the somatosensory stimulation to the hypothalamic OXT release. The spinal–supraspinal pathways responsible for somatosensory stimulation mainly comprise the posterior column pathway and spinothalamic pathway. These impulses are further relayed to the thalamus and ultimately sent to the primary somatosensory center of the CNS. Additionally, collateral connections relay these impulses to other brain areas, including the brain stem, periaqueductal gray (PAG), and hypothalamus.

4. Anti-stress Effects of Acupuncture

Depression related to mental disorder is highly associated with acute and/or chronic stress. Daily, we encounter various types of stress. Accumulation of daily life stress often causes mental disorders. Stress stimuli, both acute and chronic, may promote different physiological and neuroendocrine disorders.

CRF neurons are mainly located in the hypothalamus's paraventricular nucleus (PVN). Acute stress promotes CRF release, activating the hypothalamic–pituitary–adrenal (HPA) axis. Released CRF also affects visceral function via projecting to the autonomic preganglionic neurons at the brain

stem [17].

TENS and electroacupuncture improve various stress-induced physiological responses. Animal studies showed that sudden stress loading (acute stress) causes various abnormalities in the GI tract. Gastric emptying is delayed, while colonic transit is accelerated in rats [13, 14]. In rats, GI dysmotility (delayed gastric emptying and accelerated colonic transit) induced by acute stress is restored by electroacupuncture at ST-36. Electroacupuncture stimulates parasympathetic activity while it inhibits sympathetic activity following acute stress loading in rats [15]. These suggest that acupuncture improves the imbalance of autonomic function under acute stress in rats [15].

5. Acupuncture Treatment for Depression

Patients with depression are often prescribed selective serotonin reuptake inhibitors (SSRIs). Due to the serotonin (5-HT) hypothesis, which posits reduced levels of serotonin in the central nervous system (CNS) in depressive disorders, SSRIs are expected to elevate 5-HT levels in the brains of patients with depression.

However, previous studies suggest that the magnitude of benefit of pharmacological treatment of SSRI may be minimal or non-existent in patients with mild or moderate depressive symptoms [18]. Moreover, a recent systematic umbrella review suggests that there is no evidence to support the hypothesis that depression is caused by decreased serotonin activity and levels [19]. Serotonin metabolite, 5-HIAA, and plasma serotonin showed no association with depression. The conclusion drawn is that there is no support for the hypothesis that decreased serotonin activity or concentrations cause depression [19]. Thus, pharmacological treatment, especially SSRI, is now losing its scientific background.

In contrast, it has been proposed that acupuncture is a possible non-pharmacological treatment for depression. To compare the effects of electroacupuncture and SSRI in depressive patients, an 8-week controlled clinical study of 60 patients was performed. Electroacupuncture showed more remarkable improvement in feelings of despair, anxiety, somatization, and global clinical impression than the SSRI group [20].

An RCT study compared SSRI alone versus SSRI together with manual acupuncture or electroacupuncture in 477 moderate-severe patients with depression. Compared with SSRI alone, enhanced therapeutic effectiveness, accelerated response to treatment, and reduced adverse effects of SSRI. This suggests that acupuncture has therapeutic effects on these patients [21].

Acupuncture may act in various ways, stimulating biochemical pathways and/or restoring neuronal structures in depression [9].

Synaptic plasticity is regulated, at least in part, by 5-HT. Electroacupuncture regulates the 5-HT receptor and restores hippocampus synaptic plasticity, improving depressive behaviors. Acupuncture may improve the 5-HT receptor and upregulate 5-HT content in synaptic gaps of brain regions [22].

Brain-derived neurotrophic factor (BDNF) regulates neural plasticity by promoting axons and dendrites' growth, reconstruction, and synaptic formation. BDNF also regulates synaptic transmission. Electroacupuncture could ameliorate the depression-like behaviors and promote nerve regeneration by increasing BDNF expression in the hippocampus. In addition, acupuncture also upregulated the expression of BDNF in the PFC, suggesting that acupuncture has neuroprotective effects in depression via upregulating BDNF [23].

6. Anti-stress Effects of Hypothalamic OXT

In addition to 5-HT and BDNF, OXT has been demonstrated to mediate the anti-depressive effects of acupuncture because OXT regulates social bonding and stress reduction. Previous studies suggest that acupuncture might stimulate the release of OXT, which contributes to its potential therapeutic effects [10].

Stress responses are mediated via central CRF and peripheral corticotropin (HPA-axis). OXT is mainly synthesized in the hypothalamus's supraoptic nucleus (SON) and PVN. Central OXT has been demonstrated to reduce anxiety and attenuate the HPA axis in response to both acute and chronic stress. OXT inhibits stress-induced CRF expression via $GABA_A$ receptors, producing anxiolytic effects [24].

Animal studies have shown that OXT decreases background anxiety without affecting learning and memory of a specific traumatic event. When OXT is administered centrally before fear conditioning or extinction training, there is a reduction in fear expression and an enhancement of fear extinction [25]. This suggests that increased OXT activity prevents the formation of aversive memories during traumatic events.

As mentioned earlier, acute stress loading delays gastric emptying while it accelerates colonic transit in rats [13, 14]. In contrast, repeated experience with the same stressor produces habituation or diminution of behavioral responses. Delayed gastric emptying and accelerated colonic transit observed in acute stress are recovered to normal levels following repeated stress loading for 5 days (chronic homotypic stress) in rats. This suggests that habituation is developed once the same stress is repeatedly experienced. Recovered gastric emptying following chronic homotypic stress is antagonized by central injection of OXT antagonists [26]. In OXT knockout (KO) mice, delayed gastric emptying is still observed following chronic homotypic stress, suggesting no habituation to the repeated same stress [27]. Microdialysis study showed that OXT levels are significantly increased in the effluent from the PVN in response to chronic homotypic stress [28]. This indicates that central OXT mediates the adaptation mechanism in response to chronic homotypic stress. Chronic homotypic stress upregulates OXT expression at the PVN, inhibiting CRF expression and HPA axis activity and restoring GI malfunction in conscious rats [26].

In modern society, individuals encounter various physical, mental, and social stress daily. In order to mimic complex stress exposure in humans, rats are loaded with different types of stressors for 7 consecutive days (chronic heterotypic stress). In contrast to chronic homotypic stress, chronic heterotypic stress loading still results in delayed gastric emptying and accelerated colonic transit [26, 28]. Following chronic heterotypic stress, fewer OXT neurons and more CRF neurons are observed in the PVN [26]. These indicate that chronic heterotypic stress fails to adapt GI function due to increased CRF expression and reduced OXT expression at the PVN. Increased CRF and reduced OXT expression in the brain may promote depressive disorders. Therefore, it is conceivable to hypothesize that stress responses to chronic heterotypic stress would diminish once endogenous OXT expression is upregulated. Once we can habituate to daily complex stress, we may overcome the mental disorders associated with depression.

7. Stimulatory Effects of Acupuncture on Hypothalamic OXT Release and Stress Responses

Transcutaneous electrical nerve stimulation (TENS) at the ST-36 acupoint significantly improves GI dysmotility induced by chronic heterotypic stress in rats. This effect is abolished by central

injection of OXT antagonists. TENS increases the number of OXT neurons and decreases CRF-neurons at the PVN following chronic heterotypic stress [29]. These suggest that TENS activates hypothalamic OXT via the spinothalamic pathway (Figure 2). Activated OXT neurons inhibit CRF expression, resulting in attenuation and/or habituation in response to various types of stress loading (chronic heterotypic stress).

As previously discussed, individuals encounter various types of stress daily. Manual therapies, such as acupuncture, electroacupuncture, and TENS, may prove beneficial in alleviating daily stress in humans.

OXT expression stimulated by acupuncture could further activate other neurotransmitters in the brain. In the nucleus accumbens of the mouse brain, acupuncture induces therapeutic effects for autism spectrum disorder. Acupuncture first triggers the OXT system, which stimulates the release of endocannabinoids, dopamine, and serotonin [30].

Post-traumatic stress disorder (PTSD) has characteristic features, such as deficits in stress regulation and social functioning. Traumatic stress in the normal individual activates the sympathetic and adrenal system, causing a rise in noradrenaline and adrenaline levels. Traumatic stress also activates the HPA axis and elevates cortisol levels.

Clinical trials showed the beneficial effects of acupuncture for patients with PTSD. People diagnosed with PTSD were randomized to either acupuncture treatment or a cognitive-behavioral therapy (CBT) group. Compared with CBT, acupuncture significantly improved the symptoms of PTSD patients [31].

In 1993, Uvnas-Moberg et al., for the first time, demonstrated that various types of somatosensory stimulation, such as massage, electroacupuncture, thermal stimulation, and vibration, could increase OXT levels in plasma and cerebrospinal fluid in rats [32]. This suggests that acupuncture and TENS may act on OXT neurons at the hypothalamus.

OXT may reduce fear response and increase social functioning in PTSD patients. The proposition is that OXT treatment before fear extinction training serves as a comparable time point to psychotherapy in patients with PTSD [33].

Studies have demonstrated a strong association between chronic pain and depression. Chronic pain could worsen symptoms of depression, which worsens the pain sensation. Chronic pain and depression may share the same neurotransmitters and nerve pathways. Recent studies suggest that the beneficial effect of acupuncture for depression is due to its anti-nociceptive effects [34]. In addition to anti-stress effects, anti-nociceptive effects are a possible explanation for how acupuncture works to treat depression.

8. Conclusion

1. The pathogenesis of depression is thought to be the disorders of neuronal circuits and chemical balance in the brain. In animal studies, acupuncture has been shown to improve these abnormalities related to depression.
2. The magnitude of benefit of pharmacological treatment of SSRI may be minimal for depression. A recent systematic umbrella review proposes no evidence to support the hypothesis that depression is caused by lowered serotonin activity and its levels.
3. The daily life stress is highly associated with the pathogenesis of depression. Once we can habituate to daily complex stress, we may diminish the mental disorders related to depression.

4. OXT is involved in social bonding and stress reduction. OXT inhibits stress-indued CRF expression, resulting in anti-stress effects. Acupuncture stimulates the release of OXT via somatosensory stimulations.
5. For depressive disorders, acupuncture is a possible candidate as a non-pharmacological approach because of its stimulatory effects on hypothalamic OXT.

Author Contributions

The author did all the research work of this study.

Competing Interests

The author has declared that no competing interests exist.

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