

Acupuncture for Treating Depression and Anxiety

Research Project

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Certification

We certify that this study was prepared by a student (Xalat Mujahed Qadir) under our supervision at College of Education/ Salahaddin University- Erbil in partial fulfillment of the requirements for the degree of Bachelor in Biology.

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Abstract:

Acupuncture is a well-known form of Asian medical treatment and it is used not only as an effective curative method but also to prevent illness and maintain health. It is used for the production of analgesic effects; stress-related physical-mental disorders and homeostasis. Electroacupuncture (EA) stimulation, an application of electrical current on acupuncture needles, is one of the most popular types of this traditional therapy. In recent years, intensive studies have been carried out to explain the underlying mechanisms of the efficacy of acupuncture. An increase in the release of endogen opioid peptides is generally accepted to be a keystone pathway that affects the immune system after acupuncture application. EA treatment is effective for various immunological diseases including allergic disorders, infections, autoimmune diseases, and immunodeficiency syndromes. To understand the huge gap between specific skin point applications and immune responses, a vast number of accumulating data from experimental and clinical studies in the literature have been collected. This paper reviews the data to explain the updated mechanisms related to immune modulation via acupuncture therapy.

1. INTRODUCTION

Acupuncture, which has been practiced in Eastern countries for thousands of years, is now a very popular alternative therapy in Western countries. Acupuncture is the clinical insertion and manipulation of thin needles into specific body sites, so-called acupoints on the meridian, according to the ancient theory of oriental medicine. This process is believed to elicit profound psychophysical responses by harmonizing or balancing the energy and blood flow through the body (Tan et al., 2009). Electroacupuncture (EA) is a modified technique of acupuncture that utilizes electrical stimulation. A number of clinical studies have indicated that acupuncture or EA stimulation is effective for the management and treatment of immune-related diseases, including allergic disorders, infections, autoimmune diseases, and immunodeficiency syndromes (Arranz et al., 2007, Lee et al., 2008), although well-controlled randomized studies are further required.

Anxiety and depression are two of the most common psychiatric disorders (Sniezek and Siddiqui, 2013) Anxiety often includes feelings of fear, apprehension, and excessive anxiety energy. Depression, as a primary disturbance or secondary effect of anxiety disorder, manifests in feelings of emptiness, deep sadness or misery, loss of hope, and even thoughts of suicide (Sniezek and Siddiqui, 2013). Anxiety disorders are the most prevalent of psychiatric disorders and afflict 15.7 million people in the United States each year, and 30 million people in the United States (Sniezek and Siddiqui, 2013). some point in their lives. Anxiety tends to be chronic, and the individual and social burden is high. Furthermore, patients who have anxiety place a strain on the healthcare system, because they tend to present to general practitioners more frequently than to psychiatric professionals. Additional economic costs to the health care system include reduced productivity, absenteeism from work, suicide, hospitalization, prescription drugs, and emergency care (Lépine, 2002).

Depression affects *121 million people worldwide (Vieira et al., 2013) and it has been predicted to be the second leading cause of global disease burden by 2020. According to Chinese Medicine, anxiety and depression in women is the result of "complex interactions between diverse factors, many of which are not yet fully understood."(Sniezek and Siddiqui, 2013). In this review, the underlying mechanism of acupuncture-induced immunomodulation will be discussed based on the basic studies that have been published in the last 2 decades. We will, in particular, focus on the acupuncture-induced 1) reinforcement of natural killer (NK) cell cytotoxicity, 2) correction of the imbalance of Th1/Th2 cell response, and 3) neural-immune communication. Finally, future perspectives in this research field will be suggested.

2. LITRETUREREVIEW

2.1 Definition

Anxiety disorders constitute the largest group of mental disorders in most Western societies and are a leading cause of disability (Domschke, 2021). New evidence shows that anxiety disorders are becoming a global problem and that their prevalence is also increasing rapidly in developing countries (Remes et al., 2016). Anxiety disorder has become the most common mental disorder with a lifetime prevalence of 7.6% in China (Huang et al., 2019). Individuals with anxiety disorder manifest both physical and mental symptoms, which may be, and result in decreased ability, heavy economic burden, and poor quality of life (Domschke, 2021).

Anxiety is a natural response of the body to stress and it is the most common form of emotional disorder, accompanied by a constant and intense feeling of fear. Anxiety is hard to control and often impacts the daily life of patients. Anxiety is a key element of several other disorders: phobia, panic disorders, obsessive-compulsive disorder, social anxiety disorder, post-traumatic stress disorder (PTSD): separation, and illness anxiety disorders. Symptoms of anxiety are insomnia, restlessness, increased heart rate, general feeling of worry and fear, trouble concentrating, painful thoughts or memories, panic attacks, and others. Anxiety attacks are featured fear, sweating, shortness of breath, feeling dizzy or faint, worry, distress, and others.

Depression is projected to become the second leading contributor to the global burden of disease by 2020, affecting about 121 million people worldwide (Pratt and Brody, 2008). It is described as 'a broad and heterogeneous diagnostic grouping, central to which is depressed mood or loss of pleasure in most activities' (Health et al., 2011). Two systems are available for the diagnosis of depressive disorders. The International Statistical Classification of Diseases and Related Health Problems (ICD-10) uses an agreed list of ten depressive symptoms (Organization, 2007). 'Depressive episodes' are classified as mild, moderate or severe based on the number of symptoms present. Diagnoses defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) include single episode or recurrent major depressive disorder (American Psychiatric Association and Association, 1994).

Depression is a serious psychiatric illness that involves symptoms such as depressed or sad mood, loss of interest or pleasure in activities, changes in weight, difficulty sleeping or oversleeping, energy loss, feelings of worthlessness, psychomotor changes, and thoughts of death or suicide. It constitutes a major public health problem, worldwide. The World Health Organization declared that the burden of depression is expected to be second only to heart disease by 2020 (Organization, 2001). Depression includes depressive disorder (MDD), minor depression (MinD), antenatal depression, postpartum depression (PPD), childhood depression, geriatric depression, organic depression, vascular depression, drug-induced depression, poststroke depression (PSD), and depression comorbid with other diseases. MDD is common and can be disabling. Point prevalence rates of MDD are estimated at 5% to 13% for women and 2% to 8% for men (Pincus and Pettit, 2001) with an estimated lifetime prevalence of 16.2% and a 12-month prevalence of 6.6%. (O'Brien et al., 2004) Over 80% of people who die by suicide are clinically depressed in the months prior to their deaths (Bostwick and Pankratz, 2000).

According to the classic medicine the treatment for anxiety falls includes psychotherapy and medications (Domschke, 2021). According to Traditional Chinese Medicine (TCM) anxiety occurs due to excessive or heat energy in the head. Symptoms include excessive worry, insomnia and racing thoughts. Excessive amounts of caffeine can also create toxic heat in the liver and cause in turn rise in anxiety and anger. Caffeine, as an adrenal stimulant can ultimately lead to depression and adrenal exhaustion (Zhu et al., 2020)

Acupuncture can help redistribute the patient's energy, in order to improve sleep and reduce worry. If there is depression, then it is presented with stagnant energy within the body. Stagnation creates imbalances that lead to symptoms of depression, anger, melancholy, fatigue, inability to focus and a lack of inspiration. Acupuncture helps by enabling the energy to move more efficiently, creating homeostasis, balancing the organ systems, helping the person to manage stress and steady emotion.(Zhu et al., 2020)

Acupuncture can treat variety of illnesses and help people feel more balanced. Acupuncture causes production of painkilling chemicals by the nervous system and stimulate the body's own natural ability to heal and the part of the brain which controls the emotions, including anxiety. Acupuncture can slow the production of stress hormones and help the patients to have better-quality life. A lot of patients say that after just a few treatments they sleep better and have a stronger sense of the overall well- being.(Zhu et al., 2020)

2.2 Etiologies of Depression and Anxiety

The etiologies of depression and anxiety are still not fully understood. A number of theories on the biological basis of depression have been proposed (Krishnan and Nestler, 2008). The earliest of these theories relates to low levels of noradrenaline and serotonin in the synaptic clefts (Bunney and Davis, 1965). These two neurotransmitters remain the focus of much of the work subsequently carried out but other neurotransmitters may also have a role (Barros et al., 2002). Recent studies have investigated the potential role of various neuropeptides (Madaan and Wilson, 2009), the immune system (Miller, 2010) and genetic factors (Smoller et al., 2009).

2.3 Concepts of Acupuncture and Depression in Traditional Chinese medicine (TCM)

Acupuncture, a part of TCM, aims to restore and maintain health by stimulating specific points using various techniques. Diagnosis is aimed at differentiating underlying clinical and physiological imbalances and individually targeting treatment to restore adaptability and optimize function. The acupuncturist synthesizes and analyzes the symptoms and signs gathered from the history of the illness and from physical examination. For different syndromes in the same disease entity, different therapeutic methods are applied (Schnyer et al., 2001). In TCM, the proposed etiology of mental disorders is internal damage caused by the dysregulation of the 7 emotions, which are joy, anger, worry, contemplation (thinking), sorrow (grief), fear, and shock. When 1 of the 7 emotions is in excess, it may generate malfunction of related zang-fu (internal organs), resulting in mental disorder, as described in the book Nèi Jīng, 内经, commonly translated as, The Inner Canon of Huangdi or Yellow Emperor's Inner Canon (see Veith(Ilza, 1972). For example, excessive anger damages the liver, excessive joy damages the heart, excessive thinking damages the spleen, excessive grief damages the lung, and excessive fear damages the kidney.

2.4 Physiologic Mechanisms of Acupuncture for Depression

Current physiological studies of acupuncture suggest that acupuncture mediates signals that control information exchange across a network of interconnected channels, to restore adaptability and maintain balance (Stux et al., 1995). Acupoints can be thought of as interconnected nodes in this functional network (Stux et al., 1995). Psychiatric symptoms of depression and anxiety are associated with key neurotransmitters, such as 5-HT, NE, and DA, as well as endorphin hormones (Sheline, 2000). Depression may also be associated with dysregulation of the HPA axis. Several animal and human experimental studies indicate that acupuncture needling has demonstrable physiological effects and that it may modify the neural functioning currently believed to be implicated in the pathophysiology of affective disorders (Schnyer, 2011). Acupuncture is thought to influence neuroendocrine and immune systems, and it may treat depression by regulating levels of 5-HT, NE, DA, endorphins, or glucocorticoids (Wang and Wang, 2010) and by stimulating hypothalamic and hippocampic response (Lu et al., 2008).

2.5 Acupuncture enhances natural killer cell activity

NK cells constitute the third major lymphocyte population that is able to recognize and kill tumor cells and virus-infected cells without previous sensitization. These cells play a vital role in innate immune responses by providing a primary defense against pathological organisms (Moretta et al., 2008). Thus, up-regulation of NK cell activity would have a beneficial effect on immune system. A series of studies, conducted by Dr. Hisamitsu's group, demonstrated that successive EA stimulation at ST36 acupoint (once a day for 3 days) enhanced splenic NK cell activity in normal rats and mice, but not affect the population of NK cells in spleen. They suggested that the enhancing effect of EA on NK cell activity is mediated by increased levels of IFN- γ and that β -endorphin secretion caused by EA may play an important role in this process (Hisamitsu et al., 2002). A clinical study supported these results by showing that the number of CD16+ and CD56+ cells, which are closely related to NK cell activity, and IFN- γ levels in peripheral blood from healthy volunteers increased significantly after EA treatment (Yamaguchi et al., 2007). The Electro acupuncture (EA)-induced up-regulation of NK cell activity in normal animals (Rho et al., 2008). Lesion in the lateral hypothalamic area abolished the effect of EA on NK cell cytotoxicity, suggesting that the lateral hypothalamic area may be a major site for the neural-immune interaction caused by EA (Choi et al., 2002). Further, we investigated how EA treatment affects splenic NK cell activity at the transcription- al level, using oligonucleotide chip microarray analysis and post- microarray validation with real-time RT-PCR (Kim et al., 2005b), the proven powerful tool for functional genomics that provides direct information about mRNA expression levels from a large number of genes (Izuhara and Saito, 2006). The data showed that EA treatment increase expression of protein tyrosine kinase (PTK), which increases NK cell activity, through the induction of CD94/NKG2C complexes while EA decrease mRNA expression of protein tyrosine phosphatase-1 (SHP-1), which inhibits NK cell activity. It is also suggested that EA treatment increase gene expression of vascular cell adhesion molecule-1 (VCAM-1), which may play an important role in anchoring NK cell to the target cells, through the increased levels of IFN- γ (Kim et al., 2005a).

2.6 Acupuncture-induced modulation of Th1/Th2 balance

Naïve CD4+ T cells can be differentiated into distinct subpopulations, Th1 and Th2 cells, on the basis of their patterns of cytokine production. In general view, Th1 cells produce IL-2, IFN- γ and TNF- β that are primarily responsible for cell-mediated immunity or delayed- type hypersensitivity (DTH) whereas Th2 cells produce IL-4, IL-5, IL-10 and IL-13 that are mainly involved in humoral immunity. The Th1-and Th2-specific cytokines augment the development of the same subset and inhibit the proliferation and activity of the other subset. The imbalance of Th1/Th2 cell responses could be a main cause of infectious, allergic and autoimmune diseases (Woodfolk, 2006). Therefore, the modulation of Th1/Th2 balance has been a key strategy in the treatment of various immune disorders.

Several clinical studies have indicated that acupuncture or EA treatment is beneficial for allergic disorders, such as asthma, chronic urticaria and allergic rhinitis (Shiue et al., 2008). In general view, hyperproduction of IgE, in which IL-4, the key Th2specific cytokine, is mainly involved, promotes the development of those allergic disorders (Woodfolk, 2006) One of the authors in this study and his colleagues demonstrated, for the first time, that sequential ST36 EA stimulation significantly reduced the elevated serum levels of antigen- specific IgE in DNP-KLH immunized mice (i.e. artificially Th2-skewed condition) by suppressing the increase of Th2 cytokines, especially IL-4, not altering IFN- γ levels in spleen (Park et al., 2004). Such effect of EA is acupoint-specific, irrespective of frequency of electrical stimulation, since non-acupoint EA stimulation did not produce a significant effect and there was no difference in the efficacy between low-and high-frequency ST36 EA stimulations (Kim et al., 2011). In addition, we found that pre-treatment of phentolamine, an α -adrenoceptor antagonist, prevented the EA-induced suppression of IgE and IL-4 levels in DNP-KLH mice, suggesting an important role of noradrenergic signaling in the immunomodulatory effect of EA (Lee et al., 2007).

Interestingly, there have been some clinical reports that describe the positive effect of acupuncture on rheumatoid arthritis, which is believed to be one of the Th1 dominant disorders (Lee et al., 2008). Although basic studies providing the direct evidence are rare, it is likely that acupuncture or EA inhibit Th1 cell responses since several previous studies showed the inhibitory effect of acupuncture or EA on TNF- α , which is linked to the induction of Th1 responses (Wang et al., 2009) A recent study supported this view because successive ST36 EA stimulation (3 times a week for 1–2 months) reduced arthritis-incidence, prevented histological destruction of joint and downregulated serum levels of IFN- γ and TNF- α in collagen-induced arthritic mice (Yim et al., 2007). Therefore, it seems that acupuncture treatments have dual immunomodulatory effect in either Th1-or Th2-skewed conditions to maintain homeostasis.

2.7 Neural-immune interactions activated by acupuncture

It is widely accepted that acupuncture or EA facilitates the release of certain neurotransmitters, especially opioids, in the CNS and activates either of sympathetic or parasympathetic nervous systems, which elicits profound psychophysical responses including potent analgesia, regulation of visceral functions and immune modulation (Han, 2003). Interestingly, a number of brain imaging studies in animals and humans have shown that EA treatment activate the hypothalamus (Napadow et al., 2007), which is a primary center for neuroendocrine-immune modulation and also regulates activities of autonomic nervous system. As de- scribed before, we previously showed that EA-induced enhancement of NK cell activity was abolished by lesion of lateral hypothalamic area in normal rats (Choi et al., 2002). In addition, Hisamitsu's group reported that the amount of β -endorphin, which is mainly released from the hypothalamus, was significantly increased in the spleen as well as brain by EA treatment, coincided with increase of IFN- γ levels and NK cell activity, and that naloxone (a general opioid antagonist) pre-treatment markedly reduced such effect on IFN- γ and NK cells (Hisamitsu et al., 2002). It also should be noted that opioid receptors are expressed on immune cells including NK cells and opioid peptides can directly modulate immune responses of those cells (Kowalski, 1997). Taken together, it can be proposed that the activation of hypothalamus and release of endogenous opioid peptides is likely pathway of acupuncture-induced neural- immune interaction.

There has been evidence, however, suggesting non-opioid mechanisms, such as catecholamine and serotonin system, play a key role in the immunomodulatory effects of acupuncture. (Kasahara et al., 1993) already suggested that both the central opioid and nonopioid systems might be involved in the suppressive effect of EA stimulation at GV4 acupoint on delayed-type hypersensitivity. (Kim et al., 2005b) reported that the suppressive effect of EA on mRNA levels of IL-4 in spleen was not prevented by naloxone in DNP-KLH immunized mice. In the previous study using the same mouse model, we confirmed this result and further demonstrated that pre-administration of phentol- amine (α adrenoceptor antagonist) completely blocked the inhibitory effect of EA on Ag-specific IgE in serum and IL-4 production from spleen (Lee et al., 2007). Pharmacological blockade of serotonergic system also markedly attenuated such effect of EA in DNP-KLH mice (unpublished observation). In addition, our recent study showed that gene expression of serotonin receptor 3a in the hypothalamus significantly increased after EA treatment in normal rats with increased NK cell activity in spleen (Rho et al., 2008). Therefore, acupuncture treatment may affect somewhat different neural-immune signaling pathway depending on the condition (e.g. normal vs. Th1-dominant vs. Th2-dominant conditions).

2.8 Inflammation and the Repair Command

Micro trauma occurring during needling initiates secretions of histamine, bradikinin, substance P, serotonin and proteases, which lead a local inflammation. Hageman factor (Factor-XII) secretion with coagulation system, plasminogen, kinins and complement system activation, prostoglandins take part in the case. At the stimulation point, mast cell of Lewis layer and cells around the needle secrete bradikinin, histaminelike substances, heparin, adrenocorticotropic hormone (ACTH), serotonin, and protease. Their secretions cause vasodilatation, increased local permeability and local reaction. Due to high concentration of nerve endings and capillaries, these local effects are exaggerated (Looney, 2000). After vasodilatation, local edema, migration of leucocytes and mast cells secretion of cytokines (tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), interleukin-1 (IL-1)) stimulate hypothalamus to secrete CRH (corticotrophin releasing hormone). The repair command happens by means of hypothalamus-pituitary-adrenal axis: CRH secretion from hypothalamus causes ACTH release from pituitary gland for adrenal gland secretion of glukocorticoids to regulate inflammation and healing. By CRH, lymphocytes secrete corticosteroids and anti-inflammation cytokines, which are IL-2, IL-4, IL-10, TGF- beta (Cho et al., 2006). Activated macrophages, local endothelial cells, fibroblasts and lymphocytes secrete colony-stimulating factors (CSF), such as GM-CSF, G-CSF, M-CSF, TNF and IL-1 (Lewis et al., 2017).

2.9 Neuronal Immunomodulation

Acupuncture Points Through Central Nervous System (CNS) There are some theories to explain the perception of pain and transfer of stimuli through CNS. Simply, as the receptors (nerve endings) at the acupuncture points are evoked, the afferent nerves of either myelinated (A δ) fibers of mechanoreceptors or non-myelinated (C) fibers of nociceptive receptors transfer the stimuli to the dorsolateral column of the medulla spinalis (dorsal reflex, primary afferent depolarization) with its pain- inhibiting complex. Activation of nociceptive afferent fibers (pain induction started by potassium bradykinin, acetylcholine, prostaglandins) and synthesis of substance-P by small cells of spinal ganglia and the gasserian ganglion lead the pain stimuli (Bonica, 1990). It is believed that secreted encephalin causes the presynaptic and postsynaptic inhibition at the places, where the C and A δ type nerve fibers synapse in the dorsal horn (Lamina-V). By neospinothalamic and paleospinothalamic tracts to thalamus and thalamocortical tracts to cortex, the stimuli are perceived. A pain controlling system is activated to inhibit the pain signals which come into the nervous system. This controlling system is called the analgesia system. When the acupuncture needle is inserted, it stimulates the pain receptors (nerve endings) and causes the secretion of endogen opioids. These play a role in pain control. When the pain controlling system is activated, the neurons which originate from mesensephalon, periacuductal gray substance in the periventricular region sends their stimuli to the nuclei of rafe magnus and nucleus reticular paragigantocellularis (RPGC). Then, these stimuli go to the dorsolateral column of the medulla spinalis with its pain inhibiting complex. In the analgesia system, there are neurotransmitters like endorphin, encephalin and serotonin. Encephalin is secreted by most of the nerve fibers originating in periaqueductal gray substance and the nucleus of the periventricularis and terminate in the rafe magnus nucleus. Encephalin shows high affinity to opioireceptors delta and mü1(Chen et al., 1996). Encephalin which is secreted by pain stimulation is connected to the mü1 receptors and creates supra-spinal analgesia. It is also connected to the delta receptors and creates spinal analgesia. The stimulus of pain causes secretion of serotonin from nerve fibers which originate in the rafe magnus nuclei and terminate in the dorsal horn of the medulla spinalis. It also causes the secretion of encephalin from local neurons of the medulla spinalis. It is believed that secreted encephalin cause the presnaptic and postsynaptic inhibition at the places where the C and A δ type nerve fibers synapse in the dorsal horn (Lewis et al., 2017). For the segmental control, the cutaneo-visceral, cutaneomuscular and intersegmental (vegetative, stretch, polysynaptic) reflexes are important mechanisms related to 1-3 dermatomes for efficacy of acupuncture. In general, the cutaneovisceral reflex is the irritation of a skin point which influences functionally the organs connected to the neurotomes. The somatosensory inputs from the skin or muscle are involved in the control of various autonomic functions (Koizumi et al., 1980). Acupuncture application on the

back-shu points awakens the cutaneous-visceral reflexes and this causes a regulated effect on related organs. Back-shu points are used in the treatment of visceral diseases such as dysfunction of gastric motility (Li et al., 2006). On the other hand, acupuncture affects autonomic nervous system activity via the viscero-somatic reflexes. The skin and the related viscera have the same segmental innervations usually by dorsal roots, spinal nerves and nuclei. The nociceptive impulses from the affected viscera pass to the dorsal horn and then to anterior horn of spinal cord across interneurons. Visceral afferent nociceptors converge on the same pain projection neurons as the afferents from the skin and make a substantial mixing of information from these two sources of input. This cross-talk gives rise to the phenomenon of referred pain, where visceral nociceptor activation is perceived as a cutaneous sensation (Bear et al., 2006). When there is a dysfunction on the visceral organs, the viscero- cutaneous reflexes are awakened and create a pain and sense on the back-shu points related to these organs. That distress situation creates a pain and irritation on the dermatomes of the related back-shu point (Deng, 1989). For the supraspinal control, which is mentioned above, acupuncture affects cortical-sub cortical mechanisms (opioid, non-opioid, and sympathetic) in the treatment of psychiatric diseases, addictions and many pain syndromes (Looney, 2000). Concerning analgesic effect, EA application is more effective than traditional acupuncture (Wang et al., 1992). CNS and Neuroendocrine System (NES) Effects Acupuncture application effects cause changes in the concentrations of K+, Na+, Ca++ in the neurons (Deng et al., 1995), and EA application causes a great change in the of cells (Fu, 2000)action potential nerve . Mediation of endogenous opioid peptides like beta endorphin (BE) and encephalin are widely believed to be the major mechanism for the action of acupuncture (Fu, 2000). It has been determined that endomorphine-1, beta-endorphin, encephalin, and serotonin levels increase in plasma and brain tissue through acupuncture application(Tuğrul Cabioğlu and Ergene, 2005). Serotonin receptors [5-HT(1A)] activation and blockade have different effects on the immune response(Idova et al., 2006). Serotonin associates the immune system through the expression of its receptor subtypes in the immune cells. In the patients of depression, the nervous and immune systems interact and might be related to the change in the expression or function of the serotonin transporters in lymphocytes(Lima and Urbina, 2002) endorphin, which plays a role in producing the analgesic effect of hypophysis and

secretion of β -endorphin and ACTH from the anterior lob of the hypophysis (Pan et al., 1996). The endogenous opioids are connected to the opioid receptors, which are located in the central nervous system, and the surface membrane of nociceptors. They produce an analgesic effect, which is inhibited by naloxan (Pomeranz et al., 1977)and hypophysectomy(Takeshige et al., 1992) . The action of acupuncture on immunomodulation, though it is still under investigation, is mainly related to the reticular formation of the brain and the associated mediators (CRH, ACTH, cholecystokinin, bombesin, encephalin, dynorphin and etc.) to be involved in feedback controls. The reticular formation controls consciousness, cardiopulmonary rhythm, muscular-vessel tonus and are the junctions of sub cortical, autonomic and cortical functions. By the peripheral information or pain stimuli (EA, acupuncture, acupressure etc.), the reticular formation regulates consciousness at cortical level and alter peripheral organ functions via descending modulation systems.

2.10 Regulatory effects of acupuncture on immune function

Modern studies have demonstrated that acupuncture modulates multiple physiological systems of the body, including the immune sys- tem, to reestablish homeostasis by activating peripheral nerves to evoke physiological reflexes (spinal and supraspinal reflex) and the brain central integration (Wei-Xing, 2019). The experimental research on the effects of acupuncture on immune function can be traced back to the middle of the last century (Pan et al., 2021). Studies over the decades have shown that acupuncture has a wide range of regulatory effects on the immune system (Pan et al., 2021).

2.11 Enhancement effects of acupuncture on immunity under physiological conditions

Most of the early studies showed that acupuncture enhanced immunity of normal humans or physiological model animals (Johansen et al., 2004). Acupuncture can enhance the innate immune functions. For example, a large number of studies in rodent models (Rho et al., 2008) showed that EA at ST36 (Zusanli) upregulated the function of natural killer (NK) cells and macrophages, which play a central role in the innate immune response, especially in killing virus-infected cells. Acupuncture also increases the weight of mouse

thymus (Pan et al., 2021), suggesting an effect of enhancing innate immune function. The effect of acupuncture on adaptive immunity is also supported by many experimental results. Acupuncture can increase the number of lymphocytes in the peripheral blood and the lymphocyte transformation rate in animals (Cao et al., 1982) and humans (Jong et al., 2006). In the aging animal model, acupuncture increased the functions of T lymphocytes (Liu et al., 2009). It has been reported that acupuncture for 20 days can increase the level of IgG and IgM in the elderly (Pan et al., 2021). A few studies have shown that the lateral hypothalamus plays a role in the enhancement effect of EA. EA increased natural killer cell activity in the spleen, correlating with the activation of hypothalamus (Rho et al., 2008). Selective destruction of the lateral hypothalamic area (Choi et al., 2002) cancelled various immune enhancement effects of acupuncture. The general enhancement effects of acupuncture on immunity might benefit the prevention of infections and immune suppression status of sepsis. However, acupuncture effects on immunity show state-dependent features. For example, under disease conditions, the effects of acupuncture might be different from that under normal conditions, which is elaborated below.

2.12 Bidirectional regulations of immune function by acupuncture under pathological conditions

Previous studies have shown that the most interesting feature of acupuncture is the bidirectional regulation effect on the body's homeostasis, either in hyper- or hypofunctional states (dual regulation, normalization, or restoring homeostasis) in either patients or pathological models of animals (Wei-Xing, 2019). For instance, EA at ST36 showed stimulation of stress-induced delayed gastric emptying and inhibition of stress-induced acceleration of colonic transit (Iwa et al., 2006). Such state-dependent effect also is observed on immune modulation by acupuncture. Acupuncture can enhance the suppressed innate immune functions, such as up-regulating the decreased function of NK cells and macrophages (Johnston et al., 2011). Conversely, acupuncture can also downregulate the activity of these immune cells and related cytokines when they are in a hyperactivity state such as inflammation (see the following section). Studies (Pan et al., 2021) also showed that acupuncture has bidirectional regulating effects on adaptive immunity, such as T lymphocytes functions. T helper cells, a type of T lymphocytes, play an important role in the immune modulation. There are two main subsets of T helper cells, Th1 and Th2, which respectively produce Th1 type cytokines (e.g. IL-2, INF- γ) and Th2 type cytokines (e.g. IL-4, IL-10). The former tends to produce the pro-inflammatory responses, and the latter, anti-inflammatory responses. The balance of Th1/Th2 is changed in different diseases and that can be modulated by acupuncture (Silvério-Lopes and da Mota, 2013). For example, acupuncture can downregulate Th2-specific cytokines (Kim et al., 2011) to improve Th2 dominant disorders, such as allergic rhinitis (Shiue et al., 2008) and chronic fatigue syndrome (Yu et al., 2014). In contrast, for the Th1 dominant disorders such as rheumatoid arthritis (Yim et al., 2007), ulcerative colitis(Tian et al., 2003) and depression (Lin et al., 2014), acupuncture can modulate the Th1/Th2 balance with inhibiting Th1 responses. Such bidirectional regulatory effects suggest some interesting mechanisms that need further study (Wei-Xing, 2019). Generally speaking, The bidirectional regulatory effect of acupuncture mirrors the activation and reinforcement of the body's self-healing or biological adaptive mechanism, which is a unique effect that no specific drug can reach at this time.

2.13 The anti-inflammatory effect of acupuncture

There is growing interest in the anti-inflammatory effect of acupuncture in the research field. In recent decades, the anti- inflammatory effects of acupuncture in septic animals and patients are highlighted. The most common problem of immune response in sepsis is a hyper-reactive cytokine storm (Silvério-Lopes and da Mota, 2013) systematically evaluated 67 relevant papers published between 2001 and 2011, and concluded that acupuncture and EA are effective in modulation of immunity in animals and humans. (Lai et al., 2020) systematically reviewed 54 studies up to May 2019 on acupuncture at ST36 (Zusanli) for the treatment of the experimental sepsis in animal models crossing species (rodents and rabbits). They used 17 criteria to estimate the study quality and risk of bias. The average quality scores of the studies is 6.3 varying from 2 to 9.5, with 13 studies (15%) accepted quality scores \geq 7.0. Those studies support that acupuncture benefits to protecting multiple organs against injuries by sepsis and maintaining the immune balance to attenuate inflammation. A very new study (Liu et al., 2020), published in Neuron online, July 2020, further confirmed that acupuncture has a reliable anti-inflammatory effect, and revealed new features and mechanisms by using genetic strategy.

Conclusion

Over the last decades, treatments of either invasive applications or wide-radical surgeries have been changing into less-invasive techniques, and "if possible" drugs possess fewer side effects by means of technical improvement. For the developing need for nil-side effects and non-invasive treatments, in the future, acupuncture treatment and some sort of complementary medicine modalities seem to be much more popular together with related clinical and experimental data support. By acupuncture application, both at CNS and plasma, an increase in levels of β -endorphin, met-encephalin, leu-encephalin, and serotonin has been observed. These neurotransmitters have immunomodulatory effects on the immune system. For all of these above effects, acupuncture can be applied for immunerelated diseases and reduce risks of infection and tissue repair.

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