

Review

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Acupuncture modulates the neuro–endocrine–immune network

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Summary

As a nonspecific physical stimulation, the effect of acupuncture on diseases is produced by motivating the inherent regulatory system in the body, having the characteristics of whole regulation, dual directional regulation, etc. Modern scientific researches show that body's inherent regulatory system is neuro–endocrine–immune (NEI) network. Hence,

we speculate that the regulatory effect of acupuncture may be produced through its regulation of NEI network. In this article, we reviewed the recent researches about acupuncture's effect on the NEI network, to find out the evidence of acupuncture adjusting NEI network and provide some evidences for revealing the mechanism of acupuncture.

Introduction

Acupuncture is an important part of Traditional Chinese Medicine that can be traced back to at least 2500 years ago. It plays a pivotal role of preventing and treating diseases in the thousands of years development of Chinese nation. At present, acupuncture has been a certain degree of application in the world. As the mechanism of acupuncture remains unclear, its effect is often difficult to gain wide acceptance, restricting a wider range of application.

As a nonspecific physical stimulation, acupuncture, unlike drugs, restores normal functions by motivating or inducing the inherent regulatory system in the body, not directly acting on the pathogen. Thus, the effects of acupuncture are not directly produced by acupuncture stimulation, but are mediated by various regulatory systems in the

body. This determines that the basic way of acupuncture effect is regulating the body's condition and has characteristics of whole regulation, dual directional regulation, etc.¹

Modern scientific researches have showed that the body's inherent regulatory system is neuro–endocrine–immune (NEI) network, including nervous system, endocrine system and immune system, which is the biological basis to maintain the body's homeostasis.² At present, some researches show acupuncture has a certain modulatory effect on NEI network. Hence, we speculate that the regulatory effect of acupuncture might be achieved through its modulation of NEI network. Therefore, in this article, we reviewed the related researches about acupuncture's effect on the NEI network, to find out the evidence of acupuncture modulating NEI network and provide some

evidences for revealing the mechanism of acupuncture.

Overview of neuro–endocrine–immune network

Besedovsky and Sorokin² first put forward the concept of NEI network. The nervous system, endocrine system, immune system regulate and contact with each other. They coordinate with each other, forming a organic network, which is the biological basis to maintain the body's homeostasis. When in pathological conditions, the NEI network remodeled, playing a role of self-regulation, to make internal environment tend to stability.

NEI network has the characteristics of dual directional, divergent and polymerized nature.³ The dual directional nature refers that the regulation between two system is dual directional, and the regulation can be positive or negative. The divergent nature refers that an environmental change can cause regulatory reaction of multiple systems. The polymerized nature refers that a cell can receive a variety of control signals from different systems.

Further researches indicates that nervous system, endocrine system and immune system share common signaling molecules and their affiliated receptors, including some neuropeptides, neurotransmitters, cytokines, hormones, etc. and their receptors.⁴ The cells in each system can secrete these signal molecules and at the same time the cells surface have the molecular's receptors. Hence, the common signaling molecules and their receptors constitute the molecular structural foundation of NEI network. These molecules and receptors are called the common biological language of NEI network,³ being responsible for information communication and transmission between the three systems.

Exogenous noxious stimulations affect the neuro–endocrine–immune network

Substantial evidence has shown that the skin is a neuroimmunoendocrine organ; the body skin is rich in nervous, endocrine, immune tissues structurally, and closely associated with these three systems in function. And exogenous noxious stimuli to the skin can affect the NEI network through several pathways,⁵ which provides beneficial evidences for the

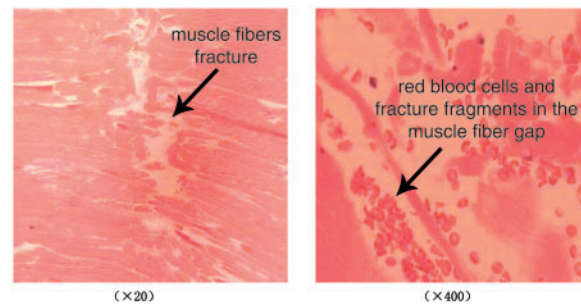


Figure 1. Pathologic picture with HE dyeing of muscle tissue at Zusanli in 10 min group after acupuncture.

exogenous noxious stimuli activating the NEI network.

Acupuncture is a traumatic physical stimulation

Recent researches demonstrate that acupuncture is a traumatic physical stimulation. Our study found that acupuncture needle could cause the muscle fibers fracture in the acupoint after inserting the needle into the acupoint, with a large number of red blood cells and fracture fragments in the muscle fiber gap and inflammatory cells infiltration (Figures 1 and 2).⁶ Thus, acupuncture can lead to certain trauma in the acupoints, which proves that acupuncture is a traumatic physical stimulation. Therefore, we believe that as a traumatic stimulus, acupuncture also can activate the NEI network, producing regulating effect.

Effect of acupuncture on neuro–endocrine–immune network system

Effect of acupuncture on nervous system

The direct feeling during acupuncture is de qi, an internal composite sensation of soreness, numbness, heaviness, distension and aching, and a radiating sensation at and around the acupoints. The sensation of de qi is most closely related to nervous system. Therefore, most of these studies focus on nervous system. Many studies have found that acupuncture can directly or indirectly activate the nervous system, causing changes of functional activities in different levels of the nervous system, and then playing its modulatory role through release of related neurochemicals.

Effect of acupuncture on neural activities

The main form of nervous system functional activities is electrical activities. Electrophysiological

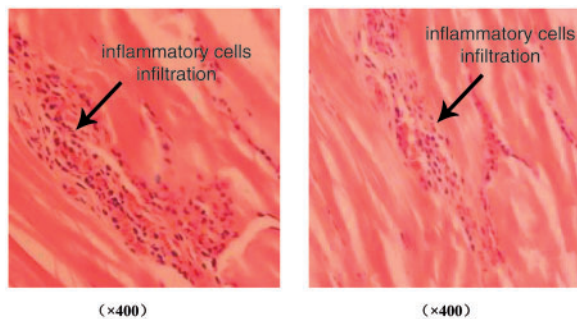


Figure 2. Pathologic picture with HE dyeing of muscle tissue at Zusanli in 6 h group after acupuncture.

studies of neural activities show that acupuncture stimulation can cause peripheral afferent nerve fibers to be excited.⁷ On one hand, the excitement could be transmitted via spinal cord⁸ to brain,⁹ and after central integration, efferent nerves¹⁰ transfer information to the target organs. On the other hand, the excitement could be transmitted through axon reflex to target organs,¹¹ eventually showing regulatory effect. Thus, acupuncture can cause discharge activities of different parts in nervous system, regulating nerve functions at different levels.

In recent years, many studies of acupuncture effect on neural functional activities have introduced advanced noninvasive neuroimaging technologies, including positron emission tomography, single proton emission computerized tomography and functional magnetic resonance imaging. These powerful imaging technologies make it possible to visualize the anatomic and functional effects of acupuncture stimulation in the brain. Studies have shown that acupuncture can cause changes of activities in different functional areas of human or animal brain.¹² It provides evidence that acupuncture can affect neurons functional activities in the brain.

Effect of acupuncture on neurochemicals

Researches carried out in the past years have shown that acupuncture can affect synthesis, release and action of several neurotransmitters (such as serotonin, dopamine, catecholamine, glutamate, acetylcholine, etc.) and neuropeptides (such as oxytocin, neuropeptide Y, cholecystokinin, vasoactive intestinal peptide, substance P, calcitonin-gene-related peptide, pituitary adenylate cyclase activating polypeptide, etc.) in both the central and peripheral nervous systems.^{13,14} The changes of neurotransmitters and neuropeptides caused by acupuncture are different due to different diseases or needling parameters.

Effect of acupuncture on endocrine system

Because of the hypothalamus–pituitary–adrenal (HPA) axis, hypothalamus–pituitary–gonadal (HPG) axis and hypothalamus–pituitary–thyroid (HPT) axis playing an important role in the endocrine activities, recent researches about the effects of acupuncture on the endocrine system more focused on these axes, with related hormones as observation indexes.

For example, acupuncture could obviously reduce hormones such as adreno corticotrophic hormone (ACTH), corticosterone related to HPA axis in chronic stress-induced rats.¹⁵ Electroacupuncture (EA) could regulate the level of uterus estrogen, pituitary follicle-stimulating hormone and luteinizing hormone and hypothalamic gonadotropin releasing hormone in ovariectomized rats, to restore the disorder of hypothalamus–pituitary–ovary axis.¹⁶ Acupuncture could increase the level of thyrotropin releasing hormone, thyroid stimulating hormone and total three typical thyroid original acid in chronic fatigue rats, to restore the inhibition of HPT axis.¹⁷ All these studies suggest that acupuncture can modulate the function of HPA, HPG and HPT axes.

Effect of acupuncture on immune system

Effect of acupuncture on local immunomodulation of acupoint

Modern studies have found that after inserting the needle into the acupoint, traumatic inflammation occurs in the acupoint, activating the local immunomodulation at the acupoint.¹⁸ Our studies also showed that acupuncture could initiate mast cells to gather in the acupoint, secreting bioactive substances such as histamine, bradikinin, SP and serotonin. These secretions caused vasodilatation, increased local permeability and local reaction. At the same time, inflammatory cell infiltrated, cytokines (IL-1 β , IL-6, IL-8, TNF- α and IL-4) and adhesion molecules (E-selectin and L-selectin) increased in the acupoint. These changes led a local inflammation in acupoints.⁶

Effect of acupuncture on nonspecific immunity

Numerous researches have shown that acupuncture can regulate the nonspecific immune function,¹⁹ including the following aspects: acupuncture can improve the number and function of phagocytes, increase the number and activity of natural killer (NK) cell, promote the synthesis, secretion and biological activities of cytokines and adjust the content of serum complement.

Effect of acupuncture on specific immunity

Studies have shown that acupuncture has certain regulating effect on both cellular immunity and humoral immunity.^{20,21} The influence of acupuncture on cellular immunity mainly include that it can promote the proliferation of T cells, improve the ratio of CD4⁺ T cells/CD8⁺ T cells and modulate the synthesis and secretion of cytokines in the immune response. The effect of acupuncture on humoral immunity mainly includes the following aspects: it can modulate the synthesis and secretion of various kinds of immunoglobulin and promote T-helper lymphocytes secreting cytokines.

Effect of acupuncture on neuro–endocrine–immune network

With the development of researches, scholars have found that acupuncture has modulating effect on the nervous, endocrine and immune systems. A researcher proposed a hypothesis, that was ‘the bidirectional positive regulatory role of acupuncture was achieved by neuro-endocrine-immune network’.²² Subsequently, several researches about acupuncture effect on NEI network were carried out, with related indicators of the three systems such as neurotransmitters, endocrine hormones, immune cells or cytokines as observed indexes.

Ju *et al.*²³ conducted the related research at the early time. It’s about acupuncture analgesia, finding that there was a NEI regulatory loop in the acupuncture analgesia. In addition, human studies have also indicated that acupuncture can modulate the NEI network. Liu and co-workers²⁴ found that acupuncture can regulate the concentration of plasma IL-2, prostaglandin E2, bright enkephalin and NK cell activity in patients with rheumatoid arthritis. These suggested that acupuncture could modulate the NEI network.

Further studies showed that acupuncture could also modulate some common signaling molecules of NEI network. For example, EA could promote T-cell immune responses in aging rats, with several common signaling molecules of NEI network involved in, such as serum IL-6, hippocampus IL-6R, hypothalamus β -endorphin and corticotropin-releasing hormone, ACTH and corticosterone of HPA axis.²⁵ But it remains to be studied that how acupuncture modulate the common signaling molecules.

Conclusion

As the body’s inherent regulatory system, it manifests dual directional, divergent and polymerized

characteristics during the progress of maintaining the body’s homeostasis.⁸ These characteristics are very similar to the acupuncture’s features of whole regulation, dual directional regulation. This also provides some basis for that acupuncture effect might be achieved through its modulation of NEI network. As a traumatic physical stimulation, acupuncture might play its role with the assistance of the body’s inherent regulation system, which determines there is a certain limitations of the acupuncture effect. Therefore, if we can clarify regulating role of acupuncture on NEI network, it’s beneficial to explain the characteristics of acupuncture effect from the perspective of modern science, and also can provide some basis for illuminating the common link of acupuncture mechanism.

These studies show that acupuncture has certain modulatory effect on NEI network. But at present, lots of related studies more focus on a single system, always paying little attention to study the three systems as a whole. And many current researches about acupuncture effects on NEI network choose some indexes of nervous, endocrine and immune system or part of their common signaling molecules as observation object, it remains lacking of overall grasp and systematic research on NEI network. Due to the close interrelation among the three systems, acupuncture modulatory effect on NEI network still need further studies. Therefore, future researches should be conducted from the integrative and associated perspective, to clarify the modulating effect and mechanism of acupuncture on NEI network.

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