

Acupuncture Regulating Neuro-Endocrine-Immune Network System

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Acupuncture can regulate the release of neurotransmitters, neuropeptides and hormones by stimulating the neuroendocrine system. In addition, acupuncture can also indirectly affect the immune system by regulating the neuroendocrine system, specifically embodying the substances released by the neuroendocrine system acting on the corresponding receptors of immune organs and immune cells. As benign stress, acupuncture can change the concentration of certain neurotransmitters, including monoamines and acetylcholine. As the main neurotransmitters of sympathetic nerves, the concentration of monoamine neurotransmitters in the blood can be significantly increased by sympathetic neurostimulation, thus affecting the immune system.

Keywords: acupuncture ; neuro-endocrine-immune network ; mechanism ; bidirectional regulation ; microenvironment

1. Introduction

Acupuncture, originating in China, can be traced back to more than 2500 years. It is one of the most time-honored treatment methods and an indispensable component of Traditional Chinese Medicine. It is practiced by inserting and twisting acupuncture needles in multiple directions and speeds, aiming to cure diseases under the theory of traditional Chinese medicine. Currently, acupuncture has been accepted to a certain extent throughout the world. According to the traditional medicine strategy of the World Health Organization (WHO) (2014–2023) ^[1], 183 countries around the world have launched acupuncture projects. However, it is challenging to obtain a widespread understanding of its effect. The unclear mechanism of acupuncture impedes its extensive application. Compared with Western medicine, acupuncture is a physical stimulus that restores normal function by adjusting the internal environment and rebuilding physiological homeostasis, instead of directly acting on the pathogen. Besides, acupuncture is both holistic and bidirectional ^[2]. This also makes summarizing the mechanism of acupuncture based on a single factor or system impossible. The neuro-endocrine-immune network was not proposed until the 20th century ^[3]. Under the dominant control of the central nervous system, the body's functions can be coordinated and regulated through the integration of the neuro-endocrine-immune networks. The body can then respond adaptively to the stimulation of the internal and external environment to maintain a steady state. Following this novel concept, the primary research into acupuncture has gone further. At present, several studies have reported that acupuncture can regulate the body's function through adjusting the neuro-endocrine-immune network. Therefore, in this article, we review the relevant studies on acupuncture's effects on the neuro-endocrine-immune network to find evidence that acupuncture regulates the neuro-endocrine-immune network and reveal the mechanism underlying acupuncture.

2. Characteristics of Acupuncture

Acupuncture is a kind of physical stimulation that can stimulate or induce the function of the internal regulation system and restore the physiological and biochemical processes to normal. Acupuncture fully exploits its stimulation effect on the physiological and pathological processes of the body and the reaction of these effects in vivo to regulate the organism. The characteristics of acupuncture include bidirectional and benign regulation, holistic and comprehensive regulation, self-limiting regulation and quality regulation ^{[4][5]}.

Holistic and comprehensive regulation means that acupuncture can regulate the body at multiple levels and targets, including the multi-target regulation of the same organ and multi-organ or multi-system regulation of the body's overall state, which is the fundamental reason for the extensive indications of acupuncture. For instance, the treatment of irritable bowel syndrome by acupuncture is the multi-target regulation of the same organ, as mentioned above. Its treatment involves a variety of active substances such as cholecystokinin and vasoactive intestinal peptide, which are involved in the regulation of gastrointestinal function at different levels ^[6].

The self-limiting regulation of acupuncture can be illuminated from two aspects. Firstly, the regulating ability of acupuncture is limited and can play a role only within the normal range of physiological regulation. Secondly, the regulating capacity of acupuncture depends on the integrity of the relevant tissue structure. Under normal circumstances, the intensity of a drug's therapeutic effect increases with an increase of drug dose, which will eventually result in off-target effects. However, the regulating effect of acupuncture presents a saturation characteristic, that is, the self-limited regulation of acupuncture [7].

Broad applications with a low risk of adverse reactions are the advantages of acupuncture, which are closely related to its characteristics. To develop research ideas and to improve its curative effect, it is important to understand the characteristics of acupuncture.

3. Mechanisms of Acupuncture on the Neuro-Endocrine-Immune Network

Acupuncture can regulate the release of neurotransmitters, neuropeptides and hormones by stimulating the neuroendocrine system. In addition, acupuncture can also indirectly affect the immune system by regulating the neuroendocrine system, specifically embodying the substances released by the neuroendocrine system acting on the corresponding receptors of immune organs and immune cells.

Studies have shown that acupuncture can increase the low level of acetylcholine in patients with Parkinson's disease and dementia as well as promote the production of acetylcholine in intracerebral hemorrhage rats with reduced acetylcholine release [8]. According to the research, acupuncture at GV-20 and K-11 in the treatment of Alzheimer's disease resulted in increased levels of plasma acetylcholine, which is one of the biological mechanisms [9]. In addition, the mechanism of acupuncture at BL-13 in the treatment of allergic asthma in rats is also related to the inhibition of the synthesis and release of acetylcholine [10]. Therefore, whether acupuncture can affect the immune system by regulating acetylcholine is worth exploring further.

As mentioned above, acupuncture can affect the immune system by regulating the neuroendocrine system. Meanwhile, acupuncture is also able to influence the neuroendocrine system by modulating the immune system. A large number of studies have shown that acupuncture has a benign regulatory effect on the immune system, involving innate immunity and acquired immunity.

At the end of the last century, the novel concept of "acupuncture serum" was advocated, which refers to the serum collected from the human or animal body after acupuncture treatment. The serum is appended to another system as an effective substance and then observed for its effect after contact with the organ, cell, or molecule in vivo or in vitro [11]. There is an assortment of bioactive substances contained in acupuncture serum, such as antibodies and immune factors, which all have an important influence on the nervous system, immune system, cardio-cerebral vascular system, etc. Acupuncture results in the release of cytokines, hormones and neuromodulators and neurotransmitters in the blood and these can have physiological effects on cells and tissues [12][13].

4. Deficiencies and Prospects of Acupuncture

Recent research has illuminated that the human body is a complex system, which is not a superposition of simple systems but rather formed by integrating different networks [14]. Acupuncture reveals the occurrence and development of diseases from a macro, holistic, and systematic perspective. It has been discovered that acupuncture is an effective physical stimulus that can act as a "promoter" to activate local cell functions and neuroreceptors, regulate the release of related chemicals in the microenvironment and how they affect each other, and further activate the neuro-endocrine-immune system. Therefore, it is challenging to summarize the mechanisms of acupuncture in previous studies using a single system. Increasing numbers of researchers are exploring the network and the complexity of the crosstalk between different systems. At present, the effect of acupuncture on various diseases has been confirmed by numerous studies, but most of them are statistically comparative studies. The depth and breadth of the research on its mechanism are still insufficient. The research level mostly stays on the therapeutic effects and cell level, while the research on the molecular mechanism has not yet been thoroughly explored. Meanwhile, the effects of acupuncture on the interaction between various cells and cytokines under the neuro-endocrine-immune system are also unclear. Recently, researchers have realized the close links between different systems and different organs, and acupuncture has performed a regulating effect on some key mediators of these systems. However, the specific mechanism of acupuncture on the interaction between these different systems has not been studied clearly. In addition, research on the transition from basic research on the functional mechanism of acupuncture to clinical practice is still scarce.

The development of systems biology and omics techniques has become a new trend in the network regulation and acupuncture therapy research. Several years of research have shown that acupuncture has immediate and delayed therapeutic effects. The immediate effect is mostly related to the signal transmission of the nervous system, while the subsequent effect is associated with the transmission of hormones, cytokines and other signals in body fluids. A variety of functional proteins can be produced through the body fluid pathways, which may lead to changes in proteomics. At the level of gene expression regulation, the transcriptomics technology can analyze the specific expression factors and biological mechanisms of acupuncture treatment against diseases. This will help to clarify the specific pathological and physiological regulation characteristics of acupuncture integrally. Metabolomics, starting from the final metabolites, traces the relationship between the metabolic changes of sugars, proteins and lipids in organisms and the occurrence and development of diseases. It can also track the time-effect relationship between the disease and acupuncture treatment as well as reflect the overall changes of the organism. Currently, with the advancement of metabolomics research, the metabolic targets of common clinical diseases treated by acupuncture are becoming clearer. The continuous improvements of the emerging analysis approaches of biological information, such as tracer technology, two-photon technology and cryo-electron microscopy technology, have also provided great convenience to acupuncture research. Therefore, the combination of the evolving omics technology and the emerging analysis methods of biological information may facilitate the study of acupuncture and enable the mechanism of acupuncture on the neuro-endocrine-immune network to be revealed intensively.

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