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Review

Acupuncture and immune modulation

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ABSTRACT

Acupuncture is probably the most popular alternative therapy practiced in the United States, Europe and many Asian countries. It has been applied clinically for more than 5 thousand years according to the ancient oriental medical theory. A great deal of acupuncture research has been achieved, with particular efforts toward understanding the pain control effects. In addition to the analgesic effect of acupuncture, an increasing number of studies have demonstrated that acupuncture treatment can control autonomic nerve system functions such as blood pressure regulation, sphincter Oddi relaxation, and immune modulation. Although only a limited number of controlled studies have assessed the efficacy of acupuncture, increasing clinical evidences support that EA treatment is effective for various immunological diseases including allergic disorders, infections, autoimmune diseases and immunodifficiency-syndromes. This review will address the mechanism of acupuncture in modulating various immune responses and the relationship between acupuncture mediated immune regulation and neurological involvement.

Contents

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 (Kaptchuk, 2002; Lee et al., 2008; Park et al, 2004; 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 immunodifficiency-syndromes (Arranz et al., 2007; Biernacki and Peake, 1998; Joo et al., 2000; Lee et al., 2008; Ye et al., 2002), although well-controlled randomized studies are further required.

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, the future perspectives in this research field will be suggested.

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2. 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; French and Yokoyama, 2003). 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; Sato et al., 1996; Yu et al., 1997, 1998). 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).

Our previous studies also confirmed the EA-induced up-regulation of NK cell activity in normal animals (Choi et al., 2002; Kim et al., 2005a,b; 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 transcriptional level, using oligonucleotide chip microarray analysis and post-microarray validation with real-time RT-PCR (Kim et al., 2005a,b), 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,b).

3. 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 (Abbas et al., 1996; Maggie, 1998; 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 (Biernacki and Peake, 1998, Chen and Yu, 1998; Jianli, 2006; Ng et al., 2004; Shiue et al., 2008). In general view, hyperproduction of IgE, in which IL-4, the key Th2-specific cytokine, is mainly involved, promotes the development of those allergic disorders (Maggie, 1998; 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., 2009). 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; Wang et al., 2007; Zherebkin, 1997). 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 (Aoki et al., 2005; Tian et al., 2003; 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.

4. 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, 1987, 2003; Filshie and White, 1998; Lundeberg et al., 1991; Mori et al., 2002; Sato et al., 2002).

Interestingly, a number of brain imaging studies in animals and humans have shown that EA treatment activate the hypothalamus (Chiu et al., 2001, 2003; Hsieh et al., 2001; Napadow et al., 2007), which is a primary center for neuroendocrine-immune modulation and also regulates activities of autonomic nervous system. As described 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 (Yu et al., 1998; 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; Stefano et al., 1996). 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 non-opioid systems might be involved in the suppressive effect of EA stimulation at GV4 acupoint on delayed-type hypersensitivity. Kim et al. (2005a,b) 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 phentolamine (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).

5. Perspectives and conclusions

Emerging evidence indicates that EA treatment elicits not only enhancing innate immunity but also modulating adaptive immune system. However, the mechanisms behind the action of EA on classical Th1/Th2 skewed diseases such as asthma, urticaria, and rheumatoid arthritis are not fully understood. For example, it is quite difficult to explain that same EA treatment could correct immunologically opposite conditions either in Th1 or Th2 dominant disorders. Recently, the pathogenesis of asthma and autoimmune diseases are closely correlated with another T cell compartments, Th17 and regulatory T cells. Th17 cells are believed to be a key player in progression of both allergic and autoimmune diseases, whereas regulatory T cells play in pivotal role in suppressing overwhelmed activation of both Th1 and Th2 cells so that alleviating allergic or autoimmune responses. The elucidation of relationship between EA and these cell types could possibly support the more detailed mechanism of EA on immunological disorders. Another key question remained in this field would be the nature of connection between EA-neuronal network and immune modulation: Does EA share the same neuronal network to elicit immune regulatory effects? What kinds of neurotransmitters are involved in immune regulation by EA? Are EA stimulation parameters for immune modulation the same as used in other EA mediated effects such as analgesia? Obviously there are more questions than answers in this field. Future studies in these issues enable us to understand the importance of acupuncture therapy in immune regulation and will lead to a novel therapeutic alternative for treating various immunological disorders.

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