

Acupuncture- Mediated Activation of the Cholinergic Anti-Inflammatory Pathway- A Review of the Literature

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Abstract

Immune system plays a pivotal role in protecting the body from pathogens, as well as from various insults, and consequently in maintaining homeostasis. Acupuncture has been used for many centuries in Asia but also, over the last decades, in Western countries, as a treatment modality for various diseases and disorders. Recent advances have shed light on the mechanisms of action of acupuncture treatment and there is now evidence that it can activate the so called “cholinergic anti-inflammatory pathway”, especially through modulation of the vagal tone. We present available experimental data, to date, regarding acupuncture’s effects on the immune system through the cholinergic anti-inflammatory pathway.

Introduction

Human body has an embedded immune system that is responsible for its protection against invading pathogens or tissue injury [1]. Keeping a balance between pro-inflammatory responses (that mediate inflammation) and anti-inflammatory mechanisms (that prevent excessive inflammatory responses) is vital to maintain homeostasis [2,3]. Production and release of cytokines (proteins produced by immune cells) is a key element in mediating inflammation. Most known cytokines include tumor necrosis factor (TNF), interleukin (IL)-1, IL-6 and high mobility group B1 (HMGB1) [2,4]. On the other hand, a neural pathway referred to as the “cholinergic anti-inflammatory pathway” plays a major role in suppressing inflammation.

In most cases immune system manages to eliminate exogenous or endogenous threats and restore homeostasis. When this is not achieved, inflammatory responses can lead to an uncontrolled tissue damage. Specifically, overproduction of cytokines has been implicated in the pathogenesis of various diseases, including Crohn’s disease, Alzheimer’s disease, multiple sclerosis, diabetes and rheumatoid arthritis, but also in conditions such as endotoxemia and sepsis [5-8]. Recent evidence suggest that vagus nerve can regulate inflammatory responses through the cholinergic anti-inflammatory pathway,

resulting in decreased TNF production and thus, in suppression of inflammation [1,3,9,10]. Acupuncture, an ancient treatment modality originating from China, is under extensive research over the last decades, regarding its mechanisms of action and recent experimental data suggest that it can mediate its effects through the cholinergic anti-inflammatory pathway.

Experimental Data

The vagus nerve has been shown to mediate immune function regulation by the central nervous system through a pathway called “cholinergic anti-inflammatory pathway” [11]. Vagus nerve fibers synapse at the celiac-superior mesenteric plexus ganglia and they modulate splenic nerve activity through the activation of nicotinic acetylcholine receptor [12]. Consequently, splenic nerve releases norepinephrine that acts on adrenergic receptors of B and T cells of the spleen, which in turn produce acetylcholine [13,14]. Finally, increased acetylcholine levels inhibit proinflammatory cytokine release by macrophages, acting on their nicotinic receptors [15].

Unilateral vagotomy in rats abolished the protective effects of electroacupuncture (EA) pretreatment in a lethal endotoxemia experimental model [16]. Moreover, systemic

administration of mecamylamine (a nicotinic antagonist) also blocked the protective effects of EA, but atropine methyl nitrate (a muscarinic antagonist) systemic administration failed to block EA protection [16]. However, direct delivery of atropine methyl nitrate into the brain resulted in complete reversal of EA's protective effects. These results indicate that the central muscarinic receptors are important elements of the peripheral cytokine production pathway [16].

Severe burns or trauma patients often exhibit gastrointestinal ischemia and paralysis that can lead to dysfunction of the intestinal epithelial barrier and consequently to multiple organ failure [17]. Various experimental animal studies have shown that electrical stimulation of the vagus nerve might exert a protective anti-inflammatory effect on the intestinal barrier activity after burn injuries through activation of the cholinergic anti-inflammatory pathway [18,19]. However, electrical stimulation of vagus nerve in humans is rather complicated since it requires a surgical approach often associated with untoward side effects, such as serious tissue injury. Acupuncture at particular acupoints (such as ST36) has similar effects to those of vagus nerve activation [18,19]. Recent animal studies in rats after scald injury have shown that EA at ST36 acupoint significantly increased gastrointestinal mucosal blood flow, while plasma diamine oxidase (DAO) and intestinal permeability were significantly decreased compared with the control group [20-22]. However, these protective effects of EA were abolished after intraperitoneal atropine injection or vagotomy, suggesting that EA acts, at least in part, in the presence of intact vagus neurenteric innervation through the activation of the cholinergic nerve pathway [22].

It has been suggested that acupuncture-mediated activation of the cholinergic anti-inflammatory pathway involves acetylcholine release from vagus nerve that binds to $\alpha 7$ -nicotinic receptors ($\alpha 7$ -nAChRs) on macrophages and thus, inhibits the release of proinflammatory cytokines [10]. However, there are reports that vagal immuno-modulation by EA might also be mediated by dopamine release [19].

EA at bilateral ST36 acupoints has been shown to significantly decrease plasma concentration of TNF- α , but did not affect IL-10 levels [23]. However, after bilateral cervical vagotomy EA at ST36 failed to decrease the concentration of TNF- α , suggesting that EA acts through the activation of cholinergic anti-inflammatory pathway [23].

EA at ST36 acupoints induces a significant effect on central nuclei of the vagus nerve, such as the dorsal nuclei of vagus nerve, solitary tract, nucleus of solitary tract and ambiguous nucleus [24]. Neurons of cornu dorsale medullae spinalis could receive afferent somatic messages from ST36, which in turn are transmitted to the nucleus of solitary tract (the splanchnic sensory nucleus), thus affecting stomach motility and electrical release by efferent vagus nerve. EA at ST36 can also excite

efferent vagus nerve fibers and increase the frequency and value of electrical discharge [25].

EA at PC-6 acupoint significantly increases vagal activity, as measured by spectral analysis of heart rate variability [26,27]. EA at LI-4 acupoint has also been shown to increase vagal tone (vagus nerve activity) through somato-autonomic reflexes that activate brain muscarinic receptors [28,29]. However, there are reports that EA at LI-4 acupoint increases sympathetic tone, as indicated by blood pressure elevation and increased renal and adrenal nerve activities, which means that certain acupoints can have dual effects on both the sympathetic and parasympathetic systems [30,31].

Discussion

Immune system plays a major role in maintaining homeostasis and acupuncture has been recently shown to regulate inflammatory responses through the activation of the cholinergic anti-inflammatory pathway. Understanding immune system innervation can provide modern medicine with new tools to prevent, as well as treat immune-mediated disorders and diseases such as rheumatoid arthritis, Crohn's disease, Alzheimer disease, multiple sclerosis etc. Recent advances in neuroradiology and immunohistochemistry have revealed new pathways and mechanisms of action of acupuncture treatment and have particularly shed light on its immunomodulatory effects. Activation of cholinergic anti-inflammatory pathway may be one of the most important mechanisms of EA-mediated anti-inflammation and organ protection.

Conclusion

Acupuncture and, especially its more potent form electroacupuncture, have been proved to exert anti-inflammatory actions, at least in part, through the activation of the so called cholinergic anti-inflammatory pathway. Therefore, acupuncture should be part of the armamentarium of each physician treating patients with immune-mediated disorders, since it could affect disease progression and thus, improve quality of life.

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