Acupuncture for Asthma: Its Potential Significance in Clinical Practice

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ABSTRACT

Acupuncture has been used for the prevention and treatment of asthma. However, the mechanisms underlying the effects of acupuncture in asthma are not fully understood. This article discusses the possible mechanisms underlying the effects of acupuncture in the prevention and treatment of asthma. Existing evidence has shown that acupuncture might facilitate the prevention and treatment of asthma via its anti-inflammatory effects. Acupuncture has been shown to modulate Th1/Th2 balance, block inflammatory cells and mediators, improve airway remodeling, and regulate hypothalamic–pituitary–adrenal axis function. Acupuncture appears to exert its antiasthmatic properties through multiple pathways.

Keywords: acupuncture, asthma, mechanism, prevention, treatment

INTRODUCTION

ACUPUNCTURE HAS BEEN SHOWN to be effective for preventing and treating several kinds of diseases, including allergic disorders, infections, autoimmune diseases, and immunodeficiency syndromes.¹ Acupuncture has been traditionally used to treat allergic asthma and chronic bronchitis in China for more than a thousand years.² Asthma is the most-common cause of chronic disease in childhood. Millions of people worldwide suffer from asthma, and the deaths related to this disease predominantly occur in low-income countries. Thus, effective treatment and complete control of asthma is very important for saving lives.³

Asthma is characterized by several respiratory problems, such as wheezing, coughing, shortness of breath, and a feeling of tightness in the chest.⁴ Asthma is a chronic inflammatory disease commonly accompanied by increased production of eosinophils, mast cells, immunoglobulin E (IgE), mucous

hypersecretion, subepithelial fibrosis, and airway hyperresponsiveness.⁵ In a patient showing acute exacerbation of chronic asthma, increased levels of neutrophils are found in the airway,⁶ leading to various degrees of structural changes and airway remodeling.^{5,7} The airway thickening is associated with airway hyperresponsiveness, treatment resistance, and the severity of asthma.⁸

The National Institutes of Health of China has confirmed the validity of acupuncture treatment and has recommended its use as an alternative therapy in a comprehensive asthma-management program. Acupuncture has a regulatory effect on the mucosal and cellular immune systems in patients with asthma.² The mechanism underlying the effects of acupuncture on asthma and the reasons behind acupuncture-point determination for treatment remain unclear to date. This article reviews current evidence supporting the role of acupuncture in ameliorating the symptoms of asthma and elucidates acupuncture's use as a complementary treatment in clinical settings.

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EFFECTS OF ACUPUNCTURE IN ASTHMA TREATMENT: CURRENT EVIDENCE

A number of studies have reported that acupuncture has anti-inflammatory effects in animal models of asthma as well as in humans. These effects include reducing the numbers of inflammatory cells, such as neutrophils and eosinophils,^{8–10} regulating the adaptive immune system (i.e., maintaining the balance of T-helper cell activity, reducing the levels of proinflammatory cytokines, and promoting the production of anti-inflammatory cytokines),^{11–15} ameliorating signs of airway remodeling,¹⁰ and regulating hypothalamic–pituitary–adrenal (HPA) axis function.⁹

Effects of Acupuncture on the Inflammatory Response

Previous studies have shown that acupuncture can reduce the number of inflammatory cells. Carneiro et al. reported that electroacupuncture (EA) at GV 14 (*Dazhui*), BL 13 (*Feishu*), EX-B 1 (MDC 1, *Dingchuan*), LU 1 (*Zhongfu*), CV 17 (*Danzhong*), ST 36 (*Zusanli*), and SP 6 (*Sanyinjiao*) resulted in a reduction in the total cell counts and percentages of polymorphonuclear cells, such as neutrophils and eosinophils, as seen from a bronchoalveolar lavage sample. EA also reduced the inflammatory cell infiltrate in peribronchial and perivascular areas.⁸ Manual acupuncture (MA) at GV 14, BL 12 (*Fengmen*), and BL 13 suppressed airway hyperresponsiveness and inhibited elevation of total leukocyte, neutrophil, lymphocyte, and eosinophil counts in bronchoalveolar lavage fluid.⁹ In addition, Nurwati, et al., reported, in 2019, that MA at BL 13 and ST 36 could reduce the numbers of inflammatory cells, such as neutrophils and eosinophils in the blood, in a mouse model of chronic asthma.¹⁰

Effects of Acupuncture on the Adaptive Immune Response

Acupuncture has been suggested to regulate the immune system. T-helper cell type 1 (Th1) plays an important role in cell-mediated immunity, whereas T-helper cell type 2 (Th2) is responsible in humoral immune responses, such as regulating immunoglobulin G (IgG) and IgE secretion. Acupuncture has been shown to restore the equilibrium between Th1 and Th2 activity by reducing the production of Th2-specific cytokines, such as interleukin (IL)-4, IL-5, and IL-13,^{11,12} increasing Th1 levels, leading to secretion of interferon (IFN)- γ ¹³; reducing the levels of proinflammatory cytokines, such as tumor necrosis factor- α (TNF- α), IL-1 β , and IL-33¹⁴; controlling T-regulator (Treg) levels in the suppression of Th2 and Th17, which produce IL-17¹⁵; and reducing the levels of IgE.^{11,12,16}

Park et al. suggested that acupuncture reduced the serum levels of IgE and Th2-specific cytokines, such as IL-4, IL-5, and IL-13, in a mouse model of asthma,¹¹ while Kwon et al. indicated that acupuncture affected the activity of cluster of

differentiation (CD)4⁺ CD25⁺ Fork box P3 (Foxp3⁺) Treg. Acupuncture improved Treg function by suppressing other T-cells and limiting the responses of the immune system, and suppressed formation of antigen-IgE complexes as well as production of IL-4, IL-5, and IL-13.¹² Moreover, 1 study in male Wistar rats showed that acupuncture at GV 14, BL 13, EX-B 1, LU 1, CV 17, ST 36, and SP 6 not only increased the levels of IL-1 and IFN- γ but also reduced the levels of IL-4 and IL-10 in the rats' bronchoalveolar lavage fluid and pulmonary tissue.¹³

A number of studies have highlighted the effects of acupuncture for reducing levels of proinflammatory cytokines. MA at BL 13 and ST 36 significantly reduced blood levels of IL-17 in ovalbumin-induced asthmatic mice.¹⁵ Other studies used different acupoints, such as GV 14, BL 12, and BL 13, as reported by Wei et al., who found that acupuncture at these points could regulate the activity of Th17, Tregs, and the nuclear factor (NF)- κ B pathway, resulting in inhibition of airway hyperresponsiveness and inflammation.⁹ Subsequently, other researchers found that acupuncture treatment also inhibited secretion of TNF- α , IL-1 β , IL-5, and eotaxin in serum.¹⁶ Furthermore, Dong, et al. showed that acupuncture reduced the concentration of proinflammatory cytokines, such as TNF- α , IL-1 β , and IL-33, as well as levels of CD4⁺ IL-17A. Yet, acupuncture increased serum levels of secreted suppression of tumorigenicity 2 (ST2).¹⁴ In humans, acupuncture at these acupoints led to a reduction in the secreted immunoglobulin A and total IgA levels in saliva and nasal secretions of patients with allergic asthma, reduced serum levels of IgE and the interleukin (IL)-2 receptor (IL-2R⁺) Limfosit T, and increased CD3⁺, CD4⁺, and CD8 levels in these patients' blood.²

Effects of Acupuncture on Airway Remodeling

MA at BL 13 and ST 36 was shown to ameliorate the signs of airway remodeling in a mouse model of chronic asthma. Acupuncture treatment for 2 weeks significantly reduced the thickness of the bronchial epithelium and smooth muscle and reduced the number of Goblet cells in the bronchioles.¹⁰

Effects of Acupuncture on HPA Axis Function

According to Wei et al., MA at GV 14, BL 12, and BL 13 in asthma models could both attenuate airway inflammation and regulate HPA activity.¹⁶ In chronic inflammatory conditions such as asthma, the level of endogenous cortisol escalated in relation to proinflammatory cytokine release, which caused hyporesponsiveness of the HPA axis. This probably occurred because of negative feedback mechanisms. Acupuncture could reduce the counts of immune cells such as lymphocytes and proinflammatory cytokine secretion, which could also shift the hyporesponsiveness of the HPA axis and promote an increase in corticotropin-releasing hormone (CRH) levels.¹⁶

Determination of Acupoints

There are several considerations when determining the acupuncture points that should be used for asthma treatment and prevention. Among the most common acupoints used are the “*Shu* point” for the Lung, BL 13¹⁷; the acupoint of the dorsal root ganglion (C-7–T-5); specific *Back-shu* acupoints, such as EX-B 1, GV 14, BL 12, BL 13, BL 14 (*Jueyin Shu*), and BL15 (*Xinshu*)¹⁸; the paravertebral points located at the levels of T-1–T-8 that regulate respiratory organs; and acupuncture points in the neck area to stimulate the vagus nerve to relax the bronchus and

absorb mucus.¹⁹ A summary of the methods including the acupuncture points used in asthma studies is provided in Table 1.^{2,8–16,20,21}

DISCUSSION

Current evidence shows that acupuncture treatment can ameliorate the signs of asthma. There are several possible mechanisms that might underlie the antiasthmatic effects of acupuncture. These include the effects from acupuncture

TABLE 1. METHODS OF ACUPUNCTURE TREATMENT IN ASTHMA STUDIES

References	Subjects	Acupoints	Methods	Results
Park et al., 2004 ¹¹	Mice BALB/c female	ST 36	EA, 3–5 V, 1 Hz, 20 min at 7, 14 & 21 d	Reduced serum IgE and decreased proinflammatory cytokines (IL-4, IL-5 & IL-13)
Carneiro et al., 2005 ⁸	Rats Wistar male	GV 14, BL 13, EX-B 1, LU 1, CV 17, ST 36 & SP 6	EA, 52 Hz & 1 mV, 20 min, 2 wks.	Reduced inflammation
Carneiro et al., 2010 ¹³	Rats Wistar male	GV 14, BL 13, EX-B 1, LU 1, CV 17, ST 36 & SP 6	EA, 20 min, 52 Hz & 1 mV, 2 wks	Minimized inflammatory response by reducing Th1/Th2 cytokines, NO & leukotriene B4 modulation
Choi et al., 2010 ²⁰	Human	CV 22, LU 5 (<i>Chize</i>), ST 40, EX-B 1, BL 13 & LI 4 (<i>Hegu</i>),	MA, 3×/wk for 4 wks with a 2-wk follow-up	Alleviated asthma symptoms & improved quality of life
Kwon et al., 2012 ¹²	Mice BALB/c female	ST 36	EA, 3–5 V, duration 0.25 ms & 1 Hz for 10 min, for 10 d in a row	Improved Treg function & reduced pro-inflammatory cytokine levels
Yang et al., 2012 ²	Human	GV 14, BL 12 & BL 13	MA, 10 min 3×/wk for 5 wks	Reduced IgA, IgE & proinflammatory mediators
Nurwati et al., 2015 ¹⁵	Mice BALB/c female	BL 13 & ST 36	MA, 2×/weeks, for 8 weeks	Decreased proinflammatory cytokine IL-17
Wang, et al., 2010 ²¹	Rats Sprague–Dawley male	GV 14 BL 12 & BL 13	MA, once every other day for 2 wks	Endogenous glucocorticoid was not involved in antiasthmatic effect of acupuncture
Wei et al., 2017 ¹⁶	Mice BALB/c female	GV 14, BL 12 & BL 13	MA, 30 min, each day for 4 wks	Attenuated airway inflammation & regulated HPA axis activity
Dong, et al., 2018 ¹⁴	Mice BALB/c female	GV 14, BL 12, & BL 13	MA: each day for 2 wks	Suppressed airway hyper- responsiveness, chronic inflammation & mucous secretion; increased lung compliance; & decreased airway resistance & concentrations of proinflammatory cytokines
Nurwati, et al., 2019 ¹⁰	Mice BALB/c, female	BL 13 & ST 36	MA, 2×/weeks, for 8 wks	Reduced inflammatory response & controlled airway remodeling

EA, electroacupuncture; V, volts; min, minutes; d, day(s); Ig, immunoglobulin; mV, millivolt; wk(s), week(s); Th, T-helper; NO, nitric oxide; MA, manual acupuncture; ms, millisecond(s); Treg, T-regulator; mo, month; IL, interleukin; NF- κ B, nuclear factor kappa-B; HPA, hypothalamic–pituitary–adrenal.

FIG. 1. Mechanism of action of acupuncture in asthma. (1) Acupuncture stimulation through local inflammation reaction. (2) Segmental stimulation of acupuncture. (3) Acupuncture causes central stimulation through the hypothalamic–pituitary axis ($\rightarrow$ stimulate and ∇ inhibit). CRH, corticotropin-releasing hormone; ACTH, adrenocorticotropic hormone; IL, interleukin; cAMP, cyclic adenosine monophosphate; ATP, adenosine triphosphate.

stimulation through local inflammation reactions, effects from segmental stimulation, and central stimulation through the HPA axis. A schematic description on the mechanism of action of acupuncture in asthma is depicted in Figure 1.

Acupuncture Stimulation Through Local Inflammation Reaction

Asthma occurs when allergens or antigens enter the endobronchial epithelium, where they are captured and presented by antigen presenting cells such as dendritic cells to activate Th0. Th0 will then differentiate into Th1, Th2, Treg, and Th17,^{22,23} leading to a Th2-dominant imbalance in the Th1/Th2 level.²⁴ Th2 cells play a central role in the allergic inflammatory response by releasing IL-4 and IL-13 (which stimulates B-cells to secrete IgE), IL-5 (which is involved in eosinophilic inflammation), and IL-9 (which stimulates mast-cell proliferation).²⁵ When the body is exposed to the same antigen again, IgE that has been expressed on the surface will bind to the antigen. IgE-antigen binding stimulates mast-cell

degranulation, which causes an allergic response.²⁶ Mast-cell granulation leads to the release of mediators such as histamine, cysteinyl-leukotriene, and prostaglandin D₂; eosinophil chemotactic factor-A; several kinds of cytokines, including TNF- α , IL-1, IL-4, IL-5, IL-6, and IL-13; and enzymes, such as chymase and tryptase. These mediators can cause inflammation, bronchoconstriction, and mucous hypersecretion.^{24,25}

Th2 cells also produce IL-5 that increases eosinophil production.^{25,27} Subsequently, eosinophils secrete transforming growth factor (TGF)- β , IL-4, and IL-13; and TGF- α activates epithelial cells, synthesis of the extracellular matrix, and mucous hypersecretion. Activated eosinophils release toxic proteins called major basic proteins and eosinophil cationic protein that cause tissue destruction.^{28,29}

Th0 cells are induced into Th17 by IL-6, IL-23, and TGF- β .³⁰ Subsequently, Th17 cells produce IL-21, IL-22, and IL-17. The IL-17 stimulates epithelial bronchioles to secrete β -defensin-2, intercellular cell adhesion molecule-1, IL-8, CXCL1, chemokine ligand-20, granulocyte colony-stimulating factor, mucin (MUC) 5 subtype B, and MUC5AC. Acupuncture also

stimulates the smooth muscles of the airway to produce IL-6 and IL-8.³¹ In addition, IL-17 is also produced by Th2 cells.²¹ IL-17 attracts neutrophils,^{21,32} which can destroy the elastin of the airway and pulmonary tissue by producing serine protease neutrophil elastase.³³ Eosinophils, IL-17, mast cells, and neutrophils can thus cause airway inflammation, mucous hypersecretion, bronchoconstriction, and airway remodeling.³⁴

A common feature in asthma is the imbalance in the Th1/Th2 level, wherein Th2 dominates the immune response.²³ Acupuncture has been shown to maintain the balance between Th1 and Th2 levels.¹¹ The tissue microtrauma caused by acupuncture facilitates immunomodulation, resulting in vasodilatation, increased permeability, and local inflammation.³⁵ Acupuncture-induced microtrauma can stimulate the production of Th1 cytokines,¹¹ which is responsible for producing IFN- γ , IL-2, and lymphotoxin.²⁷

Segmental Stimulation by Acupuncture

Allergen exposure in asthma can affect the autonomic nervous system. While acupuncture treatment can increase parasympathetic nerve-system activation, the activity of the sympathetic nerve system (SNS) is decreased. Activation of the parasympathetic nervous system in the bronchus and its branches causes bronchoconstriction, an increase in mucous secretion, and mast-cell degranulation.^{25,36}

The acupuncture points located in the thoracic vertebrae are innervated by sensory-nerve fibers of the thoracic segment of the spinal cord. Thus, stimulation of these points will activate the sympathetic nervous system (SNS) segmentally. Sympathetic nerve fibers coming out from T-1–T-4 of the spinal cord innervate the bronchus and its branches. Therefore, the segmental stimulation of acupuncture points will activate the sympathetic nerves toward the bronchus.³⁶ Activation of sympathetic nerves also stimulates the adrenal medulla to produce catecholamine, which can induce the activity of adenylyl cyclase, an enzyme required to convert adenosine triphosphate into cyclic adenosine monophosphate (cAMP). The increased cAMP level leads to relaxation of bronchial smooth muscle, inhibition of bronchial-gland secretion, and blockage of mast-cell degranulation.¹⁴ Inhibition of mast cells can normalize the production of Th2 lymphocyte.²⁷ Acupuncture can activate Tregs,¹² which will suppress the Th2 and Th17.³⁷

Acupuncture Causes Central Stimulation Through the HPA Axis

Stimulation of acupuncture points can exert its effects through activation of the HPA axis pathway.¹⁶ HPA activation induces corticotropin-releasing factor release, which then increases the production of steroid hormone from adrenal cortex. This steroid hormone can increase the sensitivity of β -adrenergic receptors, leading to the activation of the adenylyl cyclase required to produce cAMP. The increased cAMP levels result in bronchodilation, inhibition of mucous-secreting glands in the bronchus, and blockade of

inflammatory-mediator release from mast cells. Cortisol also exerts negative feedback on the HPA axis and inhibits the production of CRH–adrenocorticotrophic hormone.³⁸

Acupuncture reduces levels of several proinflammatory factors, including neurotrophin, neuropeptide, cytokines, and chemokines; and disturbs the Th1/Th2 balance via the HPA axis pathway.¹⁶ Acupuncture, via activation of the central nervous system, can reduce the production of Th2, increase levels of Th1 and restore the equilibrium of the Th1 and Th2 levels.¹

CONCLUSIONS

Acupuncture, through segmental stimulation, HPA axis, and local inflammation reaction can modulate the Th1/Th2 balance, bronchodilatation, mucous production inhibition, and blockage of inflammatory mediators from mast cells. The benefits of acupuncture in treating asthma must be determined by further research.

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CME Quiz Questions

Article learning objectives: After studying this article, participants should be able to describe some of the mechanisms of acupuncture's beneficial effect on asthma demonstrated in modern scientific research; summarize some of the anti-inflammatory effects of acupuncture demonstrated in modern research; and discuss some of the multiple physiologic pathways by which acupuncture exerts its anti-asthmatic effects.

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Questions:

1. Identify the *incorrect* answer:
 - a. Acupuncture has a long history of use to treat asthma in China.
 - b. The modern understanding of asthma pathophysiology recognizes that acupuncture is a chronic inflammatory disease.
 - c. Inflammatory processes involved in chronic asthma include increased production of eosinophils, mast cells, and immunoglobulin E.
 - d. Chronic inflammation leads to airway thickening and hyperresponsiveness.
 - e. Chronic inflammation in asthma leads to thinning of the bronchial epithelium, smooth muscle atrophy and decreased ability to secrete mucous.
2. Identify the *incorrect* answer:
 - a. Studies in animal and human models demonstrate a number of important anti-inflammatory effects of acupuncture.
 - b. Animal studies suggest that acupuncture's benefit in asthma is achieved via regulation of the adaptive immune response.
 - c. The equilibrium between Th1 and Th2 activity is a fundamental aspect of the pathophysiology of chronic asthma.
 - d. The authors point out that acupuncture may exert its beneficial effect by enhancing Th2 dominance in the Th1/Th2 equilibrium.
 - e. Acupuncture has been demonstrated in animal models to restore the equilibrium between Th1 and Th2 activity by reducing the production of Th2 specific cytokines such as interleukins IL-4, IL-5, and IL-13.
3. Identify the *incorrect* answer. Important actions of acupuncture on regulation of the adaptive immune response which have been demonstrated in the research include:
 - a. Reduced total leukocyte count and eosinophil count in bronchoalveolar lavage fluid.
 - b. Increased Th1 levels with increased secretion of interferon-gamma (IFN)- γ .
 - c. Increased anti-inflammatory cytokines IL-4, IL-5, IL-13.
 - d. Decreased inflammatory cytokines IL-4, IL-5, IL-13.
 - e. Improving regulatory T cell (Treg) function and improving Th17/ Treg balance.
4. Identify the *incorrect* answer. Some of the acupuncture techniques that have been studied in animal models of chronic asthma include:
 - a. In a mouse model, Wei and colleagues found that manual acupuncture at GV14, (Dazhui), BL12 (Fengmen), and BL 13 (Feishu) suppressed airway hyperresponsiveness and reduced total leukocyte and eosinophil counts in bronchoalveolar lavage fluid compared to controls.
 - b. Manual acupuncture at the combined points ST 36 (Zusanli) and BL 13 (Feishu) significantly reduced serum levels of IL-17.
 - c. Manual acupuncture at the points BL 13 (Feishu) and ST 36 (Zusanli) ameliorated signs of airway remodeling such as thickness of bronchial epithelium and smooth muscle hypertrophy.
 - d. Manual acupuncture at GV 14 (Dazhui), BL 12 (Fengmen), and BL 13 (Feishu) shifted the hyperresponsiveness of the HPA axis and promoted an increase in corticotropin-releasing hormone (CRH) levels.

- e. Manual acupuncture at SJ 5 (Waiguan), GB 41 (Zulinqi), and LR3 (Taichong) ameliorates airway remodeling in chronic asthma.
5. Identify the **incorrect** answer. The authors suggest that acupuncture produces its beneficial effects on asthma through several underlying mechanisms which include:
- a. Stimulation via acupuncture-induced tissue microtrauma.
 - b. Segmental stimulation of acupuncture points activate sympathetic nerve fibers which have a beneficial effect on the bronchi and adrenal medulla.
 - c. Acupuncture point needling produces a central stimulation of the HPA axis which results in bronchodilation, inhibition of mucous secreting glands in the bronchus, and blockade of inflammatory mediator release from mast cells.
 - d. Acupuncture's regulatory effect on the autonomic nervous system has a restorative effect on the gastrointestinal microbiome.
 - e. Acupuncture reduces the levels of several proinflammatory factors and restores the equilibrium between Th1 and Th2 levels.

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