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Possible Mechanisms Underlying Epipharyngeal Abrasive Therapy (EAT) with $ZnCl_2$ Solution for the Treatment of Autoimmune Diseases and Functional Somatic Syndrome

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Abstract

Chronic epipharyngitis is a common latent but serious condition that may contribute to a wide range of diseases in humans, including collagen diseases, glomerulonephritis and autonomic nervous disorders. In a previous study, we presented a putative causal role of chronic epipharyngitis in the development of functional somatic symptoms and syndromes following human papillomavirus vaccination by demonstrating a significant improvement in symptoms following abrasive therapy using $ZnCl_2$ on the epipharynx. Since this initial study, we have expanded our clinical experience, providing epipharyngeal abrasive therapy to 988 patients with confirmed chronic epipharyngitis associated with a wide variety of clinical symptoms. These symptoms could be classified into three broad categories, namely local inflammation-referred, autoimmune-related, and neuroendocrine symptoms. Symptom alleviation was achieved in the majority of patients with repeated epipharyngeal abrasive therapy.

Through an in-depth review of the literature on epipharyngeal abrasive therapy, combined with our clinical experience, we propose three mechanisms underlying the therapeutic effects of epipharyngeal abrasive therapy: the astringent anti-inflammatory effect of $ZnCl_2$, a blood-letting effect that promotes removal of epipharyngeal activated lymphocytes and drainage of excess inflammatory fluids containing various antigens, cytokines or noxious substances, and a neuromodulation effect achieved through stimulation of the vagus nerve. These effects can be explained within the context of current understanding of immunology, lymphology and neuroscience.

Our hypothesis-driven review provides a theoretical basis for the observed therapeutic effects of epipharyngeal abrasive therapy in ameliorating various diseases, including functional somatic symptoms and syndromes following human papillomavirus vaccination.

Keywords: Chronic epipharyngitis; Microcirculation; Vagus nerve; Lymphatic congestion; Human papillomavirus vaccination

Introduction

Located at the back of the nasal cavities, the epipharynx is a unique tissue that is vulnerable to the effects of upper respiratory infections and air pollution. At the same time, as a component of the nasopharynx-associated lymphoid tissue (NALT), the epipharynx plays a role in the production of memory/effector lymphocytes in response to exogenous antigens in inspired air, which contributes to host defense mucosal immunity as a source of antigen-specific IgA-producing B cells [1]. For these reasons, the epipharynx is prone to chronic inflammation, known as chronic epipharyngitis [2].

Chronic epipharyngitis has been described as a possible contributing factor to a wide variety of human immune-mediated diseases, including collagen diseases, glomerulonephritis, autonomic nervous disorders, and primary neurological disorders [2-4]. Moreover, we have recently suggested a putative link between chronic epipharyngitis and functional somatic syndrome (FSS) following human papillomavirus (HPV) vaccination [5,6]. Although chronic epipharyngitis has been implicated in a wide range of diseases in humans, the pathophysiology of chronic epipharyngitis has yet to be clarified. Moreover, most patients are usually unaware of having chronic epipharyngitis until extensive submucosal edema with altered microvessel running is identified on endoscopic examination, and confirmed by the pain and hemorrhage during epipharyngeal abrasive therapy (EAT) [2,3]. Therefore, EAT provides a diagnostic tool, as well as a specific treatment to resolve the chronic inflammation of the epipharynx.

EAT was originally developed by Horiguchi approximately 50 years ago, as part of his extensive pioneering studies regarding the involvement of chronic epipharyngitis in various diseases in humans, including autonomic nervous dysfunction, dysregulation of immunological and blood coagulation functions and psychological dysfunction [3]. Horiguchi also established the therapeutic strategy for EAT, which has the potential to remarkably ameliorate the inflammation of the epipharynx, as well as the associated health conditions.

Symptoms	No. of Patients
Inflammation-referred local symptoms	
Headache	288 (29.1%)
Post-nasal drip	177 (17.9%)
Pharyngeal discomfort	158 (16.0%)
Chronic cough	163 (16.5%)
Neck and shoulder stiffness	165 (16.5%)
Sore throat	131 (13.3%)
Nasal obstruction	42 (4.3%)
Chronic sputum	42 (4.3%)
Autoimmune related symptoms	
IgA nephropathy	88 (8.9%)
Palmoplantar pustulosis	28 (2.8%)
Atopic dermatitis	21 (2.7%)
Reactive arthritis	20 (2.0%)
Rheumatic arthritis	18 (1.8%)
Chronic urticaria	18 (1.8%)
Psoriasis	7 (0.7%)
Sternocostoclavicular hyperostosis	7 (0.7%)
Scleroderma	6 (0.6%)
Ulcerative colitis	5 (0.5%)
Neuroendocrine symptoms	
Dizziness	143 (14.5%)
Chronic fatigue	142 (14.4%)
Irritable bowel syndrome	100 (10.1%)
Stomach discomfort	80 (8.1%)
Depression	76 (7.7%)
Paresthesia	67 (6.8%)
Insomnia	66 (6.7%)
Photophobia	61 (6.2%)
Pyrexia	55 (5.6%)
Menstrual disturbance	54 (5.5%)
Generalized pain	46 (4.7%)
Restless leg	26 (2.6%)
Anxiety disorder	16 (1.6%)

Table 1: Reported symptomology among the 988 patients with chronic epipharyngitis.

His insights into the pathophysiology of chronic epipharyngitis further prompted him to hypothesize that dysfunction of the autonomic nervous system, as well as dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, might play a pivotal role in the clinical presentation of these health conditions [3].

Building on Horiguchi's academic achievement and findings regarding the treatment of chronic epipharyngitis using EAT, we have accumulated our own clinical experience with patients having chronic epipharyngitis, and confirming its significant effect in clinical practice [5]. Therefore, our aim was to discuss the possible therapeutic mechanisms of EAT, based on recent advances in medical science.

Patients, Their Symptoms and Treatment Procedure

To date, we have treated 988 patients with chronic epipharyngitis. All patients had been referred to our clinic for treatment of resistant symptoms possibly associated with chronic epipharyngitis. Prior treatment had included the use of steroids, sleep-inducing drugs, anti-anxiety drugs, nonsteroidal anti-inflammatory drugs, and vitamins. The range of presenting symptoms is summarized in Table 1, and can be classified into three broad classes, namely, inflammation-referred local symptoms, autoimmune-related symptoms, and neuroendocrine symptoms. With regard to autoimmune-related symptoms, recent pathophysiological studies have suggested that these immunological conditions might be triggered by pathogenic antigens in chronic tonsillitis which disturb the host-defense immune mechanisms [7-9]. As immunological characteristics of epipharyngeal lymphocytes are very similar to those of tonsillar lymphocytes [2], it is likely that epipharyngeal lymphocytes may play a role in triggering autoimmune diseases. As well, in many patients, more than two type symptoms were often overlapping. We treated all patients using EAT, as originally described by Horiguchi [3] with some modifications.

Briefly, we inserted a sterile straight nasal cotton swab, soaked with 0.5% $ZnCl_2$ solution, in one of the nostrils, pushing the swab in a straight direction until resistance was felt. At that point, we repeatedly prodded in various directions to converge inflamed tissue. The procedure was then repeated in the other nostril. Next, the entire epipharyngeal wall was scrubbed using a pharyngeal swab soaked with 0.5% $ZnCl_2$ solution. Some of our patients were taught to perform EAT with nasal swab at home, using the same technique, twice a day initially, and then once daily for a few years. In many patients, hemorrhage and pain on abrasion disappeared within a few months. Although the extent of the effects of EAT varied between patients, depending on the severity of their symptoms, long-term and sustained resolution of symptoms was achievable in most patients. In general it was more effective to carry out EAT more frequently. Patients were followed-up through our clinic on a monthly basis and, with the exception of a few cases, EAT was discontinued with full resolution of the original symptoms.

Putative Mechanisms of EAT

The first mechanism of EAT is the stringent anti-inflammatory effect of $ZnCl_2$. A prominent feature of the epipharynx is the presence of epithelial cells expressing MHC class II antigen [2], together with a large number of lymphocytes which are located directly adjacent to these epithelial cells, or co-located among them, indicative of the likely role of these epithelial cells in responding to antigen presentation [1,5]. In our experience, the severity of the pain on abrasion with post-abrasive hemorrhage paralleled the severity of the inflammation,

which gradually decreased in response to repetitive EAT. This indicates that $ZnCl_2$ contributes, at least in part, to suppressing inflammation in chronic epipharyngitis. The anti-inflammatory effect of Zn has also been reported in the treatment of chronic inflammatory skin diseases, such as acne or eczema, using topical $ZnSO_4$, with the therapeutic effect resulting from the inhibition of inflammatory cytokine production, including IL-1 [10]. As well, Zn gluconate lozenges have been reported to improve the symptoms of the common cold [11]. However, in our experience, the light application of $ZnCl_2$ to the epipharynx was insufficient to control symptoms, requiring the concomitant abrasive procedure to obtain significant clinical effects. This finding suggests that $ZnCl_2$ is likely to act beneath the submucosal area to inhibit the epipharyngeal-activated lymphocytes and, thus, reducing the level of inflammatory cytokines.

The second mechanism is the hypothesized blood-letting effect of EAT, which is schematically illustrated in Figure 1. Submucosal edema is a cardinal sign of inflammation and a significant characteristic of chronic epipharyngitis.

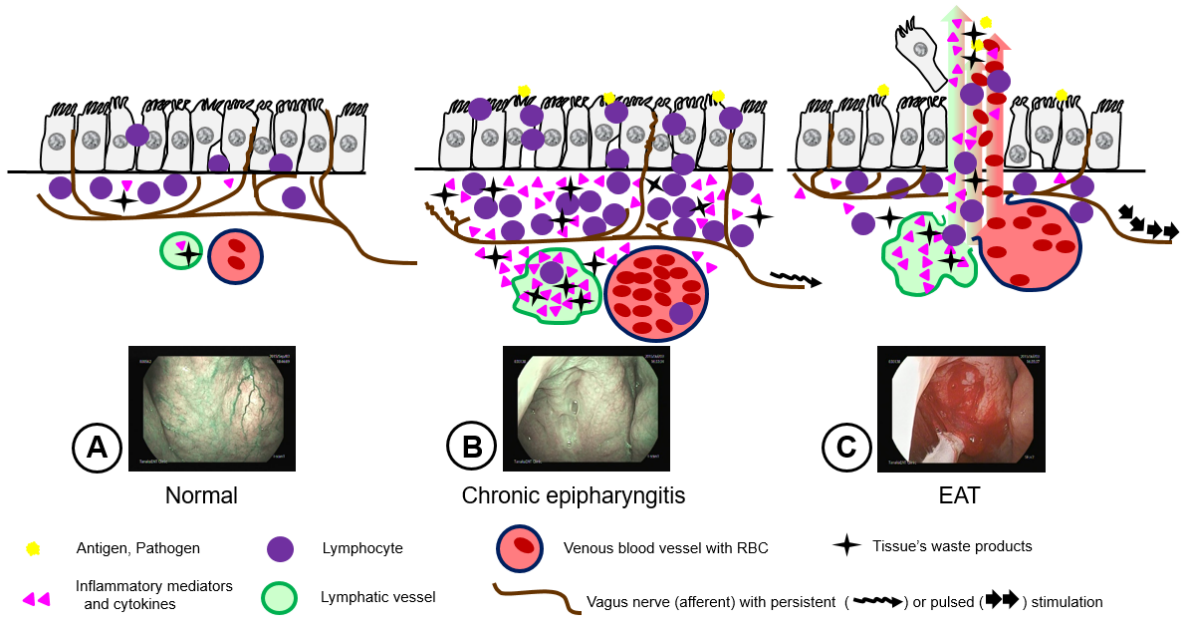

Figure 1: Schematic illustration of the hypothetical mechanisms of EAT, supported by endoscopic findings. The surface of the epipharynx is normally lined with ciliated columnar epithelial cells, with an abundance of lymphocytes in the submucosal area and co-located among the epipharyngeal epithelial cells. Venous plexus in the submucosal area is identified using image-enhanced endoscopy, with bandlimited light (A). The epipharynx is also rich in demyelinated sensory afferent nerve fibers of the vagus nerve. In chronic epipharyngitis, prominent submucosal edema blocks observation of the architecture of blood vessel (B), indicative of an impairment in lymphatic drainage and loss of homeostatic fluid balance. As a result, an increased number of immunocytes accumulate on the internal and external surfaces of the congested lymphatic and blood vessels. The stagnant blood flow results in dysfunction of vascular endothelial cells, enhancing the production of inflammatory mediators and cytokines which induces higher vascular permeability. This vascular permeability promotes exudate secretion and lymphatic dilation, further attenuating lymph drainage. The lymph stasis may further cause inefficient clearance of the tissue's harmful waste products. In this state, the terminal nerve endings of the vagus nerve may be persistently irritated by inflammatory substances, noxious chemicals and harmful antigens produced within the epipharyngeal tissue. The blood-letting effect of EAT (C) can directly excrete the excessive interstitial fluid which contains inflammatory exudates. Relief of venous and lymphatic congestion may promote recovery of normal microcirculation and efficient immune surveillance. Additionally, the pulsed and rhythmic prodding of afferent nerve terminal of vagus nerve by EAT may stimulate the cholinergic anti-inflammatory pathway via reflex neural circuits.

Since the epipharynx is an active immune site, playing a role in initiating mucosal immunity [1,2], activated T cells and memory B cells, as well as interstitial fluid containing various antigenic molecules and cell debris, are present in the submucosal area of the epipharynx [2], intended to be transported *via* collecting lymphatics toward deep cervical lymph nodes for further immune surveillance. The observed submucosal edema is indicative of an impairment of lymphatic drainage and failure of venous drainage. Under such a congested and persistent lymph stasis, more pathogenic antigens and reactive T and B cells would accumulate in the tissue, although this phenomenon might represent an attempt to compensate or maintain clearance of interstitial fluid and inflammatory infiltrates to restore homeostasis. The extent of hemorrhage during and after EAT is indicative of the congestion of the regional venous blood vasculature in chronic epipharyngitis. Therefore, it is likely that within the chronically inflamed epipharyngeal architecture, blood vessels lose their flow, forming intricate venous plexus. The resulting dysfunction of endothelial cells lining congested vessels might promote the production of inflammatory cytokines [12]. Moreover, various endothelial inflammatory mediators, such as prostanoids, histamine or nitric oxide, have all been shown to affect lymphatic drainage [13]. Collectively, therefore, in a situation of chronic epipharyngitis,

mediators of inflammation, released in the vicinity or within the lymphatic tissue, either directly or through changes in blood vessel dysfunction, would cause the prominent submucosal edema and development of the regional abnormal microcirculation. The massive bleeding caused by EAT would drain excessive interstitial fluid, which contains the tissue's waste products, harmful antigens, immune cells, and inflammatory cytokines and mediators. The relief of venous and lymphatic congestion may further improve overall circulation in the region, including arterial, venous and lymphatic flow. Moreover, recovery of an active lymphatic transport *via* collecting lymphatics toward deep cervical lymph nodes would restore efficient immune surveillance.

Recent studies have revealed a functional lymphatic drainage system of the brain into the deep cervical lymph nodes, providing drainage of extracellular fluid, which includes cerebrospinal fluid and interstitial fluid, and maintaining the water and ion balance of the brain. This system also provides a route for waste clearance, resorption of macromolecular solutes and immune surveillance in the brain [14,15]. Blockage of this lymphatic drainage system may result in a loss of homeostasis of the neuronal environment of the brain, which may contribute to impairment in neuronal function and of the immune neuroendocrine system [16,17]. As the epipharynx is rich in lymphatic vessels, it is considered to be an important path for the lymphatic drainage of the brain to the deep cervical lymph nodes [18,19]. Thus, it is likely that submucosal congestion of the epipharynx, due to chronic epipharyngitis, may block this lymphatic drainage and contribute to the development of immune neuroendocrine disorders. Therefore, the resolution of epipharyngeal congestion with blood-letting by EAT may be a factor in the recovery of neuroendocrine symptoms in patients with chronic epipharyngitis.

The third mechanism regards the effect of EAT on neuromodulation *via* stimulation of the parasympathetic 10^{th} cranial nerve (the vagus nerve, VN). The epipharynx receives autonomic input *via* the pharyngeal plexus, which consisted of afferent and efferent fibers from the glossopharyngeal nerve and VN, and sympathetic efferent fibers from the cervical ganglia [20]. The pharyngeal sensory branch of the VN has been identified in the human epipharynx [21], which may be stimulated by EAT. As an example, Horiguchi reported an effect of EAT in regulating homeostatic mechanisms to normalize either high or low blood pressure [3]. In fact, Horiguchi provided evidence that EAT could effectively control the abnormal vasoconstriction induced by mecholyl injection in humans [3]. In our practice, we have further experience of the benefits of repetitive EAT in ameliorating symptoms of stomach discomfort and irritable bowel syndrome. The transient strong cough reflex induced by EAT, particularly in patients with a chronic cough, provides further evidence of VN stimulation by EAT.

Stimulation of the Vagus Nerve by EAT

Although the mechanism by which EAT stimulates the VN has yet to be fully clarified, we speculate that this can be achieved by two mechanisms. First, the EAT-induced bleeding of the epipharynx could recover VN functions indirectly *via* suppression of the classical Reilly-Selye's phenomenon [22,23]. This phenomenon is defined as follows: a strong or long-lasting central or peripheral irritation of the autonomic nervous system can induce a systemic hemorrhage due to microcirculatory changes caused by vasomotor dysfunction (Reilly's phenomenon) [22], followed by an over-adjusted stress reaction of the whole body (Selye's stress response) [23], which involves the HPA system. In fact, the symptoms in many of our patients were compatible with those of Reilly-Selye's phenomenon. As examples, dizziness, photophobia and headache may result from the vasospasm in Reilly's phenomenon. As well, somatic discomfort, such as generalized pain, fatigue or pyrexia, menstrual disturbance, psychological symptoms (depression and anxiety) and neural symptoms (paresthesia), which are all consistent with FSS, may reflect the over-adjusted stress Selye's response. Because the epipharynx is extremely rich in autonomic nerve fibers, and considering Reilly's indication of the oral/pharyngeal area as being the most vulnerable site to induce annoyable Reilly-Selye's phenomena [22], it can be postulated that chronic inflammation of the epipharynx could induce the various aforementioned pathological health conditions. Of note regarding this issue is the recent report by Kojima et al. regarding the triggering of acute myocardial infarction by exposure to dust in Asia [24]. Asian dust contains large particles (up to 4 μm in diameter) that include harmful chemicals and microbiological materials which become trapped in the epipharynx. Thus, it is possible that acute myocardial infarction following Asian dust exposure could result from Reilly's phenomenon triggered by irritation of autonomic nerve endings in the epipharynx.

The autonomic nerve endings in the epipharynx could also be irritated by the noxious substances of chronic epipharyngitis, including inflammatory cytokines and mediators, cell debris and pathogenic antigens, which can stimulate or damage the unmyelinated autonomic nerve endings, triggering disorganized and abnormal autonomic nerve signals. The early observations by Horiguchi of abnormal fibrinolytic activity and abnormal digital vasomotor function in patients with epipharyngitis provide support for a dysregulation of microcirculation in these patients [3]. Therefore, elimination of the focal inflammation, together with removal of congested and excess blood and interstitial fluids containing various harmful molecules or substances in proximity of autonomic nerve endings, could reasonably be expected to inhibit the persistent pathological stimulation of the autonomic nervous system, with subsequent normalization of autonomic function, including that of the VN.

Second, the VN could be directly stimulated by the mechanical effect of repetitive prodding on the epipharynx (30 times in each nostril) during EAT. Neurons can be stimulated by various modalities, including light, sound, electricity, tactile stimuli and manual massage [25]. Rhythmic prodding of the epipharynx by nasal swab would, therefore, stimulate the VN. Recent studies have demonstrated that stimulation of the cervical or auricular branch of the VN, either directly by mechanical stimulation or indirectly by subcutaneous electrical stimulation, can trigger a 'broad parasympathetic effect' *via* activation of the nucleus tractus solitarii (NTS) in the brainstem [26,27]. EAT could provide an alternative method to stimulate the VN, due to the richness of VN nerve endings in the epipharynx, which would subsequently activate the NTS, which is located only a few centimeters posterior to the epipharynx. This direct stimulation of the VN, without the need for electrical devices, is a distinct advantage of EAT.

Based on the recent findings of Tracy et al. regarding the role of VN in downregulating cytokine synthesis, VN stimulation could decrease the inflammatory response in autoimmune-mediated diseases [28]. Notably, the anti-inflammatory function of VN is mediated by activation of the α7 nicotinic acetylcholine receptor on macrophages *via* splenic adrenergic inputs from T cells in the spleen [29], known as the cholinergic anti-inflammatory pathway. Accumulated evidence has confirmed significant benefit of VN stimulation in patients with various inflammatory diseases, including Crohn's disease and

rheumatoid arthritis [30-32]. Similarly, improvement in the symptoms of autoimmune diseases that we identified in our patients is likely to reflect, at least in part, VN stimulation by EAT. Moreover, as we consider the increasing view of neuromodulation as a promising avenue for the treatment of neurological disorders, modulation of the activity of the autonomic nervous system, and of the VN in particular, is a logical target for neuromodulation. Efferent VN activity provides direct input to the brainstem, and is further integrated in cortical areas for the modulation of movement, balance and sensation, as well as for the modulation of cognition and mood [33]. Functional magnetic resonance imaging has been used to demonstrate that VN activation of the brainstem is associated with a simultaneous activation of much of the cortical areas in humans [34]. In experimental animals, it has been demonstrated that afferent fibers of the pharyngeal branch of the VN project to the NTS and activate the brain [35]. Anatomical studies have further demonstrated projections from the NTS to the dorsal raphe nuclei, locus coeruleus, amygdala, hypothalamus, thalamus and orbitofrontal cortex [36]. In our experience, the fact that most neuroendocrine symptoms disappeared after EAT prompts us to speculate that EAT stimulates the VN, either directly or *via* the cortical-limbic-thalamic-striatal neural circuit, with consequent improvement in health and psychological state. The effect of psychological state might reflect the effect of VN stimulation in elevating levels of the inhibitory neuroreceptor GABA [37] and in inhibiting aberrant cortical activity within the reticular activation system [38].

Neuromodulation has recently been shown to be effective in the treatment of Parkinson's disease and multiple sclerosis, where a portable tongue neurostimulator (Portable Neuromodulation Stimulator: PoNS) is used as an interface to integrate activity of the specific cranial nerves (trigeminal, facial and possibly VN) and convey the integrated signal to the brain [39]. EAT may offer similar potential as a multi-targeted therapy that can be applied in physical medicine and neurosciences for neuromodulation. Based on our experience, we propose that further assessment of the potential beneficial effects of EAT for VN stimulation and, indirectly, on brainstem and HPA systems, is warranted.

Conclusion

Based on our experience and a review of the literature regarding the use of EAT for the treatment of chronic epipharyngitis, we provide a review of the putative mechanisms by which EAT may ameliorate symptoms of not only epipharynx inflammation but also autoimmune and neuroendocrine dysregulation. The beneficial effect of EAT appears to be attributable to the astringent anti-inflammatory effect of $ZnCl_2$, with the resultant blood-letting effect promoting the removal of epipharyngeal activated lymphocytes and drainage of excess inflammatory infiltrates and pathogenic antigens. Additionally, VN stimulation may further offer beneficial neuromodulation effects. These postulated wide-ranging effects of EAT are summarized in Figure 2. Although further researches including immuno-histochemical analysis of epipharynx are necessary to validate our hypothesis, our review provides the first proof of concept regarding the pathophysiology of chronic epipharyngitis and of the potential association between chronic epipharyngitis and FSS induced by HPV vaccination. We propose that EAT should be acknowledged as an emerging technique to promote recovery from conventional treatment-resistant human autoimmune and neuro-psychiatric diseases, as well as neuroendocrine disorders, featured by FSS.

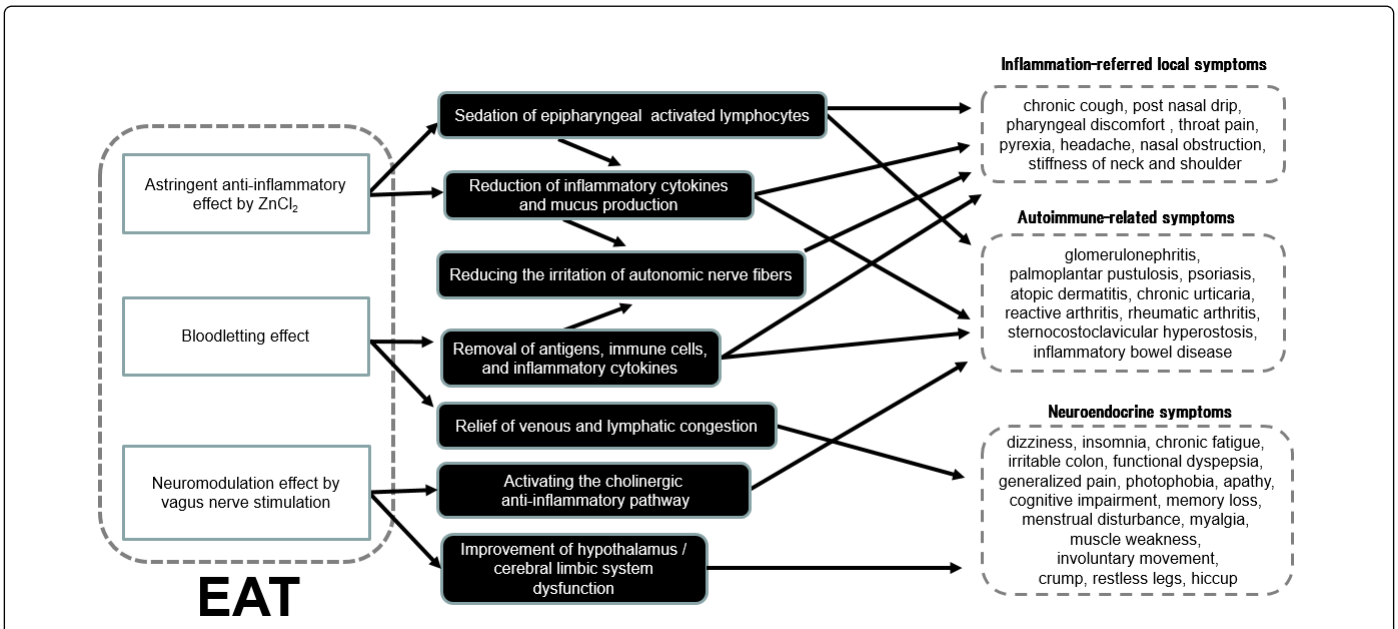

Figure 2: Possible underlying mechanism of EAT for the treatment of various immuneneuroendocrine symptoms.

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