



Acupuncture Analgesia

The anti-inflammatory effect of acupuncture and its significance in analgesia

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ABSTRACT

In the mechanisms of acupuncture analgesia, an important aspect often overlooked is the anti-inflammatory effect of acupuncture, which is mainly attained through the self-limiting inflammatory response-inflammatory reflex and its regulation of hypothalamic-pituitary-adrenal(HPA) axis and autonomic nerve system (the vagus nerve and the sympathetic postganglionic fiber). The significance of anti-inflammatory effect of acupuncture in analgesia is manifested twofold: The first, inflammatory nociceptive pain is a major type of chronic pain. The second, neurogenic inflammation is the mechanism by which certain acupoints or acu-reflex points (ARPs) are formed at the body surface and have short-cut connections to the pathological focus. Selecting ARPs and applying appropriate sensory stimulation or local microtrauma (affected by different needling means or stimulation parameters), combined with low-frequency electrical stimulation or the vagus stimulation in the concha region, are helpful to strengthen the anti-inflammatory and analgesic effect of acupuncture.

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Introduction

In the study for the mechanisms of acupuncture analgesia, the release of endogenous opioids is already well understood. However, with new discoveries of inflammatory reflex and the affirmation of the anti-inflammatory effect of acupuncture in the past few decades, acupuncture's anti-inflammatory effect in reducing pain plays an important part in its analgesic mechanisms. By reviewing the anti-inflammatory and analgesic effect of acupuncture and its mechanisms, this paper presents the significance of anti-inflammatory effect for acupuncture analgesia, and explores ways how to improve the analgesic effect of acupuncture by enhancing the anti-inflammatory effect, including the optimal selection of stimulation points, means or methods of acupuncture.

The anti-inflammatory and analgesic effect of acupuncture

The anti-inflammatory effect of acupuncture has been thoroughly studied and affirmed in many inflammatory diseases, especially in the treatment of inflammatory pain. The following are some examples related to somatic pain and visceral pain.

In a randomized controlled study, 63 patients with rheumatoid arthritis (RA) were split into two groups. One group received electroacupuncture (EA) and the other received non-EA. Acupuncture

points were selected on specific points or locations related to pain (*Ashi* points) and related *yang* meridians. The patients were treated every other day for ten treatments per course. Each patient received three courses of treatment. The researchers concluded that EA could effectively lower the contents of tumor necrosis factor- α (TNF- α) and vascular endothelial growth factor (VEGF) in peripheral blood and joint synovia to improve the internal environment for genesis and development of RA, to enhance the clinical therapeutic effectiveness [1].

The other example is chronic prostatitis-related pain, often referred to as chronic pelvic pain syndrome (CPPS). In a study [2] on 50 patients with CPPS, the levels of Interleukin-8 (IL-8), Interleukin-10 (IL-10) and TNF- α in prostate fluid were detected and the correlation between those changes and their pain score was analyzed. The positive correlation was obtained between IL-10 level and the pain score ($P < 0.05$). In addition, this study observed an effective rate of 89.4 percent for pain reduction by means of acupuncture in 47 subjects of them. As acupuncture lowered the pain levels, the levels of the cytokines (IL-8, IL-10 and TNF- α) lowered. Accordingly, the study concluded that acupuncture reduces CPPS by reducing these cytokine levels.

Anti-inflammatory mechanisms of acupuncture

To clarify the anti-inflammatory mechanisms of acupuncture, we must first review the mechanism of self-limiting inflammatory response in tissue injury. Inflammation is a self-protection

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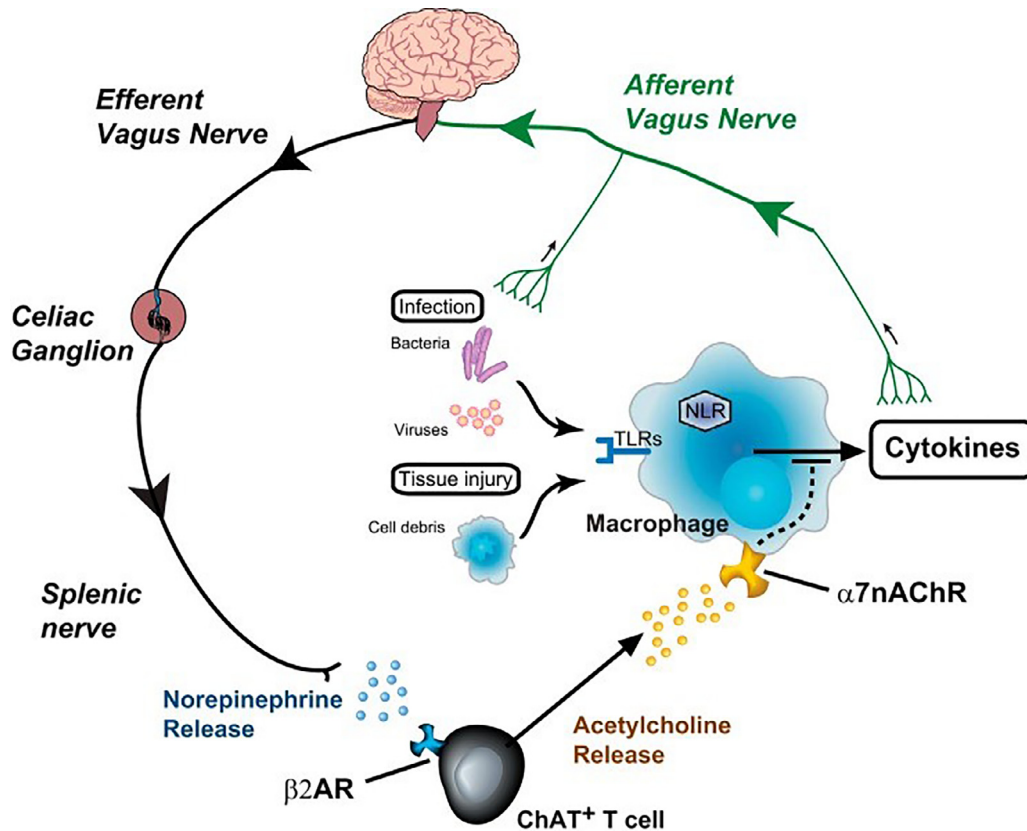


Fig. 1. The inflammatory reflex from Sundman E, Olofsson PS, 2014 [3].

response of the body. Once invasion and tissue injury occur, they are sensed by pattern recognition receptors that activate innate immune cells. This early response gives rise to a cascade of events, including the release of proinflammatory cytokines and recruitment of leukocytes, aimed to clear pathogens and ultimately restore health. It is crucially important that the immune response is regulated within narrow limits and terminated as soon as the threat has been properly addressed. Otherwise, the reaction may cause excessive tissue damage, non-resolving inflammation and inflammatory disease, and even death [3].

In recent years, it has been clear that the mechanisms of the self-limiting inflammatory response are an immune-regulatory vagus nerve circuit, also called the inflammatory reflex (Fig. 1) [4]. Specifically, it is that sensory nerve fibers, e.g., afferent vagus nerve branches, report on localized cytokine levels and inflammation in the periphery. This information is processed in the brain stem, which generates efferent signals that travel through motor fibers in the vagus nerve and activate the adrenergic splenic nerve, which releases norepinephrine in the spleen. Specialized choline acetyltransferase-expressing T cells (ChAT+ T cells) release ACh in response to norepinephrine on β2-adrenergic receptors (β2AR) and inhibit macrophage cytokine production by activating their α7-nicotinic ACh receptors (α7nAChRs) [3]. Thus, this reflex is responsible for the automatic restriction of inflammatory response. In daily life, mild inflammatory pains due to soft tissue injury, such as tendinitis caused by excessive tendon usage, often can completely self-heal as long as the suffering tendon is well rested.

As a type of non-injection stimulation, the anti-inflammatory effect of acupuncture attained by strengthening the immune response of the body can be manifested in two aspects: first, mechanical stimulation of acupuncture can regulate immune function by stimulating the hypothalamus-pituitary-adrenal (HPA) axis,

as well as sympathetic and parasympathetic pathways. Second, acupuncture itself is a type of local microtrauma on the tissues at the body surface, which can trigger or strengthen the body's self-inflammatory reflex to alleviate inflammation.

- (1) When examining the sensory reflex activated by acupuncture stimulus, it is observed that the stimulus inputs various types of sensory information by the action potential induced by acupuncture at various receptors within acupoints to the central nervous system through its corresponding afferent pathways. This information results in the activation and generation of various neuroendocrine transmitters.

- The activation of HPA axis [5]

The HPA axis governs the systemic release of glucocorticoids from the adrenal glands into the blood stream. HPA stimulation can be a successful strategy to induce the production and systemic distribution of glucocorticoids to modulate metabolic and immune responses. A typical example of its role is that acupuncture on Huántiào (环跳GB30) inhibits CFA-induced paw edema in mice through a mechanism that is prevented by adrenalectomy and glucocorticoid inhibitors. More specifically, EA on GB30 induces sciatic sensory afferent signals (SAS) activating the paraventricular nucleus (PVN) to secrete corticotrophin-releasing hormone (CRH). CRH activates the anterior lobe of the pituitary gland to release adrenocorticotrophic hormone (ACTH) into the bloodstream. ACTH activates the zona fasciculata (Fasc) of the adrenal glands to produce glucocorticoids. Glucocorticoids diffuse into the cells and release the receptor (GRs) from the inactive complex. The GRs homodimerize and transactivate anti-inflammatory cytokines such as IL-4 and IL-10. During

transrepression, GRs bind to transcription factors such as AP-1(activator protein 1) and NF-kB (Nuclear factor kappaB), and prevent them from inducing inflammatory factors.

- The stimulation of vagus nerve [5]

The vagus nerve is the principal parasympathetic nerve. Vagal stimulation modulates multiple physiological functions from digestion to inflammation. It was found that either stimulating auricular points [Wèi (胃CO4), Xiǎocháng (小腸CO6)] or somatic acupoints (e.g., Zúsānlǐ (足三里 ST36) and Nèiguān (内关PC6)) in humans increased the gastrointestinal motility via vagal stimulation. EA on ST36 also reduced serum levels of inflammatory cytokines [6] and prevents organ damage in mice with polymicrobial peritonitis induced by cecal ligation and puncture, and has been found to prevent burn-induced inflammation and lung tissue injury. These effects were mediated by the vagus. Vagal stimulation was also achieved by stimulating other acupoints, e.g., EA on “Bǎihuì (百会GV20)” and “Dàzhū (大椎GV14)” in mice with experimental ischemic stroke could improve cerebral blood perfusion and reduce brain damage, apoptosis, oxidative stress, and inflammation via vagal stimulation.

The vagus nerve is a cholinergic nerve that produces acetylcholine (ACh), which and other cholinergic agonists such as nicotine inhibit TNF- α production in murine macrophages by inhibiting the NF-kB pathway via $\alpha 7$ nicotinic cholinergic receptors ($\alpha 7$ nAChRs). Current studies suggest that, similarly to α - and β -adrenergic blockers, selective $\alpha 7$ nAChR-agonists may provide pharmacological advantages for treating inflammation. Electro-stimulation, acupuncture on auricular points can attenuate serum concentrations of inflammatory cytokines TNF- α , IL-1 β , and IL-6, as well as improving kidney and lung injury in septic rodents.

- The stimulation of sympathetic nerve [5]

Sympathetic stimulation can induce either local or systemic catecholamine secretion. The typical mechanism of sympathetic modulation is via activation of the adrenal glands to produce systemic release of catecholamines. The systemic release of catecholamines can cause adverse effects such as systemic metabolic lipolysis and immunosuppression. Recent studies have suggested that the sympathetic preganglionic nerve excitation caused by the systemic catecholamine secretion is quite different from the local catecholamine secretion by the sympathetic postganglionic nerve excitation. It has been postulated that many of the local effects of sympathetic innervations are mediated by a direct interaction of the postganglionic nerves with macrophages. The local sympathetic regulation of the immune system can provide clinical advantages for treating inflammatory disorders such as arthritis by preventing systemic immunosuppression and susceptibility to secondary infections.

Besides, it was also observed that sympathetic stimulation could induce either local or systemic catecholamine secretion depending on the electrical frequency. Specifically, high frequency EA on ST36 inhibits inflammation through preganglionic innervations of the adrenal glands in rodents. By contrast, low frequency EA on ST36 in rodents inhibits inflammation through local sympathetic postganglionic innervations, independently of the adrenal glands. In other words, high-frequency EA appears to activate preganglionic innervations of the adrenal medulla to induce systemic catecholamines, whereas low frequency EA appears to activate specific sympathetic postganglionic innervations to induce the local release of neurogenic norepinephrine.

For a long time, the functional systems of sympathetic nerve and vagus nerve were often regarded as antagonistic. Actually, they can also be synergistic. Their role in the anti-inflammatory process is such an example. In the inflammatory reflex, they are expressed as sequential connections to achieve the same goal [5].

- (2) When examining the anti-inflammatory mechanisms induced by acupuncture microtrauma, the acupuncture stimulus results in a certain degree of local microtrauma, which further activates the neuro-immune reflexes. These include mast cell involvement, the release of vasoactive substance, such as cGRP, histamine, SP, adenosine, prostaglandin, bradykinin, etc., in which, upon the activation of A- δ and C-fibers via axon reflex, resulting in vasodilatation in small vessels, increased blood flow [7], and triggered local inflammatory and anti-inflammatory response.

In 2011, a mice study affirmed that acupuncture could induce the secretion of adenosine, a neuromodulator with anti-nociceptive properties because of local microtrauma. It was observed that adenosine was released and its concentration in local tissues increased 24-fold during the 30-min acupuncture session [8]. This study suggested that the acupuncture at the affected areas is crucial for its anti-inflammatory and analgesic mechanism. Though distal acupoint selection may also temporarily relieve pain through non-specific analgesic mechanisms, stimulation at the affected areas resulting in appropriate local microtrauma often has a more pronounced effect for long-lasting inflammation relief.

Local microtrauma, i.e., since injury is usually an important cause of inflammation, why could the local microtrauma induced by acupuncture generate the anti-inflammatory effect? First, as mentioned earlier, the inflammation reflex induced by local microtrauma is a process that automatically limits inflammation. Because the source of injury (e.g., acupuncture) is removed immediately after minor stimulus, the inflammation induced by it subsides rapidly and the initial local microtrauma is repaired quickly. However, the inflammation induced by it is obviously useful in breaking the “inflammatory-anti-inflammatory equilibrium” that originally exists in the local area, which commonly exists in chronic inflammatory diseases.

In conclusion, the anti-inflammatory mechanism of acupuncture involves not only the systemic but also the local. They include stimulation of HPA axis, the autonomic nerve system (ANS), including the vagus and sympathetic nerve, as well as the inflammatory reflex caused by a local microtrauma of acupuncture (Fig. 2).

The significance of anti-inflammation for acupuncture analgesia

First, and foremost, the reason why anti-inflammation is crucial for acupuncture analgesia is because inflammatory nociceptive pain is a major type of chronic pain. Generally, commonly seen pain in the clinic can be roughly divided into inflammatory nociceptive (tissue-injury), neuropathic (nerve-injury), cancer-related and visceral pain [9]. In fact, any exogenous or endogenous injuries will eventually lead to inflammatory responses, which itself serves as the direct cause of pain. Thus, it can be said that inflammation is the core mechanism of pain.

A typical example of inflammatory pain is joint pain which occurs when a series of inflammatory factors stimulate and sensitize peripheral nerve endings. The most common is rheumatoid arthritis, which is a systemic inflammatory disease manifesting pain, swelling and stiffness of joint, especially on the small joints such as on the hand and the foot. Its pathophysiological process can be simply described as the following five points: (a) Pro-inflammatory factors recruit inflammatory cells to synovial tissue

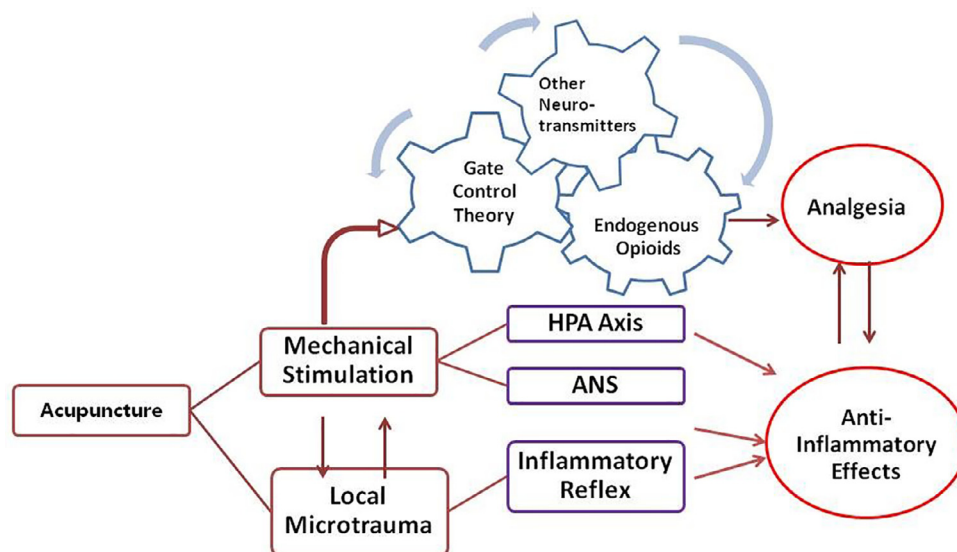


Fig. 2. Schematic diagram of anti-inflammatory and analgesic effects of acupuncture. Note: ANS – autonomic nerve system.

around the joint. (b) Prostaglandin and bradykinin directly activate nerve terminals in synovial tissue. (c) Inflammatory factors, chemical factors and growth factors sensitized peripheral nerve terminals. (d) Glutamate and excitatory neurotransmitters in pain information transmission act on receptors in joints, further leading to cascade reaction of pain. (e) In addition to the pain directly caused by inflammation, the abnormality of CNS (central nervous system) regulation mechanism and other systemic inflammation, can also lead to increased joint pain in patients [13].

For acupuncture analgesia, the significance of its anti-inflammatory effect is also reflected in the role of acupoint (stimulation target of acupuncture). It is now known that both the classical *Ashi* point and the modern recognized sensitization points or ARPs [10] have a "short-circuit" connection with the pathological focus. Their formation mechanism is often expressed as a process involved in the central sensitization or peripheral sensitization [11], that is to say, all kinds of positive reactions (tenderness or hyperalgesia, increased local tissue tension, morphological changes, elevated skin temperature, etc.) at the ARPs or *Ashi* points are actually manifestations of neurogenic inflammation [12]. Acupuncture not only could alleviate the pain but also reduce the neurogenic inflammation by strengthening the inflammatory reflex. Thus, its positive manifestation can subside (desensitization or reduced tenderness) with reduction of inflammatory pain. A typical example is that acute appendicitis is relieved by acupuncture, and the degree of tenderness at Maxwell's point in the abdomen or the *Lanwei* (阑尾 Appendix point) in the leg is also significantly reduced. In addition, this is typical example why choosing *Ashi* or ARPs often has a better therapeutic outcome better than non-ARPs.

However, presently, many clinical acupuncturists still lack sufficient recognition about the anti-inflammatory and analgesic effects of acupuncture. There are at least two types of misconception. The first, in view of the correlation between certain types of pain due to soft tissue injury and the increase of local tissue tension, some acupuncturists only noticed that the increase of tissue tension can lead to pain, while ignoring that its cause is still inflammation. Therefore, as long as the inflammation is not be under control, even if the tension of local tissues has been released via certain techniques (e.g., cutting of high tensile tissue), the temporary release of tension may have a transient pain relief, but the pain will recur easily.

The second, acupuncture is thought to be ineffective for pain caused by degenerative diseases. In fact, anatomical abnormalities are environmental factors liable for inflammation, but in most case the inflammation within or surrounding the degenerative tissues is the cause of pain. For example, it is generally accepted that mechanical pressure or mild inflammation are the main causes of osteoarthritis. Another example is inflammatory tendinitis, which can develop into tendon degeneration (decrease of collagen fibers), after a long period of time, but in the stage between the two, anti-inflammatory effect of acupuncture remains effective. Besides, in most cases, pain due to calcaneal bone spur and degenerative lesions of the spine (cervical spondylosis or lumbar hypertrophy) can be alleviated after acupuncture, although the structure abnormalities cannot be recovered. All these prove that inflammation remains the main cause of pain in various degenerative diseases.

In short, as shown in Fig. 2, when acupuncturists began to understand the underlying analgesic mechanisms of acupuncture mostly relates to the promotion of the release of endogenous opioids, they should not overlook the other important mechanism of acupuncture analgesia through anti-inflammation.

Anti-inflammatory strategies to improve clinical efficacy of acupuncture analgesia

Once the anti-inflammatory mechanisms of acupuncture is well-understood and the significance of anti-inflammation for analgesia is beyond doubt, it is now time to explore strategies on how to select proper stimulus targets (acupoints or ARPs), as well as means of needling and their stimulus parameters improve the treatment methods in line with the purpose of anti-inflammatory and analgesic effect. Here are a few ideas:

Selection of stimulus targets

Due to the higher sensitivity of ARPs than none-ARP acupoints, as well as the stronger needling sensation and reflex effect of stimulating ARPs, the systemic anti-inflammatory effect and analgesic effect via HPA axis are also significantly improved when ARPs are selected as stimulus targets. Of course, besides ARPs or *Ashi* points, many common-used acupoints such as ST36 and SP6 also have systemic anti-inflammatory and analgesic effects [13].

Table 1
Stimulation characteristics of various needling means.

	Sensory stimulation	Local microtrauma	Local cutting	Local stabbing
Filiform needle	0 to 3	1	0	+
Small knife needle	3	3	3	2
Stiletto needle	2	2	2	2
Floating needle	2	2	0	3
Giant needle	2	2	0	2
Python needle	4	4	0	4

Note: The scale of stimulation intensity is from 0 (none) to 4 (highest).

From the perspective that stimulating sympathetic postganglionic fibers is more beneficial to local anti-inflammatory effect than stimulating sympathetic preganglionic fibers, it is also advised to select *jiājī* points along the spine, because they are near the sympathetic chain, and can directly stimulate the sympathetic postganglionic fibers. Besides, the sympathetic nerve endings of the vascular wall can be stimulated by choosing bloodletting method at suffering regions with inflammatory pain.

The anti-inflammatory effect of auricular acupuncture is attributed to stimulating the auricular branch of vagus distributed in the cavum concha and the cymba concha. It has been affirmed from electrophysiology and morphology that stimulation in the concha zone can activate the auricular branch of vagus [14].

Increase the stimulation amount or the extent of local microtrauma by acupuncture

Appropriately increasing the stimulation amount or the extent of local microtrauma can be achieved by using thicker, longer or knife-shaped acupuncture needle or certain complex needling means. Because the thicker filiform needle has a larger stimulation area than the finer one, it not only stimulates the nerve endings or receptors in the stimulation target, but also has a greater local microtrauma, thus, it may induce a stronger anti-inflammatory response. In a study, forty-eight patients with chronic lumbar myofascial pain syndrome were randomly allocated to 3 groups to investigate the impact of diameter of filiform needles on the analgesic effect. Diameters of needles inserted were 0.25 mm (group A), 0.5 mm (group B), and 0.9 mm (group C), respectively. Visual analog scale evaluation and health survey were conducted at baseline and 3 months after the treatment. Results showed that efficacy of treatment with thicker needles (0.9-mm diameter) was better than that of thinner ones (0.5 mm diameter) [15]. In another study, 170 patients with knee osteoarthritis were randomly divided for needle-knife therapy group ($n=76$ completed) and acupuncture group ($n=75$ completed). After treatment, the decrements of IL-1 β , IL-6 and TNF- α in the synovial fluid and clinical symptoms in the needle-knife therapy group were greater than those in the acupuncture group [16].

In Table 1, we compared the stimulation intensity of four kinds of stimuli (mechanical sensory stimulation, local microtrauma stimulation, local incision or poking) among six kinds of acupuncture needles. The intensity of each kind of stimulus was divided into grade 0–4. For filiform needles, the sensory stimulation can be large or zero (from grades 0 to 3), and the local microtrauma stimulation is the smallest (grade 1), and there is no local cutting effect (grade 0). For needle knives and stiletto needles, there are four kinds of stimulation, with stiletto needle a bit lighter. The floating needles, giant needles and dialing needles, they have no cutting effect, and the other three kinds of stimuli can

be found, especially for the python needles, which have the largest amount of stimulation (grade 4).

Of course, the local microtrauma induced by acupuncture is related not only to needles but also to needling manipulations. In order to obtain an intense needling sensation, there are many kinds of complex needling manipulations in the clinic. For example, "tamping needle method" (meridian tamping method) is a representative needling manipulation with an intense stimulation via frequent twisting and insertion in acupoints [5], and accordingly it causes a greater injury to local tissues.

In addition, one must take into account that the degree of local microtrauma should not be over-intensive. Although greater local microtrauma stimulation can induce stronger anti-inflammatory response, it can also aggravate inflammatory symptoms, which constitutes a main reason for the aggravation of pain in some patients after local microtrauma is attained. An excessive degree of local microtrauma sometimes may form new scars, resulting in the recurrence of the pain. Therefore, it is especially important to compromise between mechanical sensory stimulation and local microtrauma stimulation.

Application of lower frequency electrical stimulation

Several recently studies shown that both manual acupuncture (MA) and EA can have a dramatic effect on both leukocytes (white blood cells) and their associated cytokines. However, blood tests revealed that EA was more effective than MA in reducing pro-inflammatory cytokines IL-6, IFN- γ , and TNF- α within test subjects that have collagen-induced arthritis and inflammation [13].

The analgesic mechanism of EA is obviously related to the frequency of electrical stimulation. Previous studies have known that EA with lower frequency (2 Hz) induces the release of enkephalins and endorphins, while EA with higher frequency (100 Hz) induces the release of dynorphins [14]. Recent studies suggest that different frequencies of EA have different effects on normal people and patients with chronic inflammation. Lower frequency (2–10 Hz) is more effective than higher frequency (100 Hz) in suppressing inflammatory pain [9]. In other words, for patients with chronic inflammatory pain and neuropathic pain, it is better to use EA with lower frequency instead of higher frequency [17].

Conflicts of interests

None.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.wjam.2019.03.003.

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