

## **The underlying neurobiology mechanism of acupuncture and moxibustion**

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### **Abstract**

Acupuncture and moxibustion are two most important managements of traditional Chinese medicine. However, their precise scientific mechanism is still unknown. Acupuncture is usually practiced on arms with three Ying and three Yang pathways and on legs with three Ying and three Yang pathways. The Ying and Yang pathways are actually co-related with the dermatome distribution on arms and legs. The analgesic effect of acupuncture is to sharply stimulate limbs to inhibit the referred pain area in the inner organs. For examples, the inner arm Ying path: Pericardium meridian is actually the T1 dermatome distribution. Thus, Pericardium meridian acupuncture can control the pain in chest including lung, heart, and esophagus. The other important concept of acupuncture mechanism is it can stimulate POMC production. The neuro-endocrine POMC can generate ACTH and endorphin. ACTH will then up-regulate corticosteroid production. Thus, acupuncture also has anti-inflammatory effects such as curing allergic rhinitis. Endorphin activation can also reduce pain and produce euphoria-like feeling. Acupuncture is mediated by sharp pain via A delta fibers. A delta fiber, stimulating sympathetic acute stress response including epinephrine and norepinephrine, can compete the accompanying slow pain/inflammation transmitting c fiber. Thus, acupuncture can suppress pain and inflammation via gate-control like mechanism. Moxibustion plays the opposite role. Moxibustion produces heat sensation which transmits via c fiber. Thus, it will facilitate the host inflammatory/immune response against pathogen infection. Thus, Huangdi Neijing said that when acupuncture is not suitable for an illness, moxibustion is suitable for the illness. Another important mechanism for acupuncture is nerve plasticity. In stroke patients, acupuncture stimulates paralyzed limb nerve re-generation and synapse re-formation. This nerve plasticity is the same as the principle of physical rehabilitation. It is worth nothing ear acupuncture mechanism. Vagus nerve distributes in the ear choncha. Thus, ear acupuncture can

also compete the inner organ pain sensation via vagus nerve inhibition as we view ear as another dermatome of inner organ.

## Introduction

Acupuncture /moxibustion are two key components of Chinese traditional medicine. However, they are still viewed as placebo effect by western society because the Ying-Yang & Wu Xing is not compatible to the modern physiology. Even they are not accepted by modern medicine, WHO still list at least 60 diseases for acupuncture indications mostly including analgesics and anti-inflammatory disorders. For examples, low back pain, tooth pain, or allergic rhinitis. Even acupuncture and moxibustion are effective in clinical medicine, there is still lacking scientific mechanism for the two useful tools. In clinical practice, chronic pain such as low back pain or chronic inflammation such as allergic rhinitis are not easily controlled by medications. The side effects emerge as drug dosage increases. Thus, simple tools such as acupuncture and moxibustion can aid clinical management for chronic pain and chronic inflammation effectively.

## Mechanism of Chinese medicine philosophy

In Chinese medicine, there is BaGang(The eight outlines). Physicians need to distinguish Ying/Yang, External/Internal, Cold/Hot, Weak/Strong. Internal or External just distinguishes if the disease is from inner organs or outer tugmen. Usually, acupuncture or moxibustion stimulating the outer tugmen can control the referred pain of inner organs. This mechanism will be explained later. Cold or hot means if heat/thermal set-up points are dys-regulated. Heat shock proteins and fever are body mechanism to initiate host immune response against pathogens. Thus, cold means low immunity and hot means overactive immunity. This is related to the treatment of moxibustion. Weak/Strong and Cold/Hot are actually co-related with overlapped symptoms. Weak means low immunity and strong means overactive immunity. However, cold or hot is more related to acute immune reaction and weak or strong is more related to chronic immune reaction. Acupuncture and moxibustion mediate their actions via modulating immune responses. Ying/Yang is the summary of the above symptoms. Yang includes external/strong/hot and Ying includes internal/weak/cold.

## Mechanism of acupuncture

Even acupuncture is very effective in clinical medicine, the underlying mechanism of acupuncture is still unknown. Here, I will propose a principle for acupuncture. There are six meridians (three Yang & three Ying) in arms and another six meridians (three Yang & three Ying) in legs. The distribution of these meridians is actually the distribution of dermatomes. (Chapple 2013, Sanchez-Araujo, Luckert-Barela et al. 2014) Acupuncture mediates its action via controlling referred pain. The dermatome is reflecting the embryology relation to the inner organs. For example, T1 dermatome is the Ying side of arms which is the same as Pericardium meridian. Neiguan belonging to The Ten Key Acupoints is controlling the chest organs (Neiguan for heart & lung). T1 dermatome reflects the cardiac plexus innervated organs. Coronary heart disease usually causes referred pain radiating to the inner middle arms, especially left limb. On the contrary, if we perform acupuncture on Pericardium meridian (T1 dermatome), we are able to inhibit the pain originated from the cardiac organs. It could be due to the pain transmission competition between the "External" dermatome and the "Internal" inner organs from the same embryonic origin. We can also use this principle to apply to other useful Ten Key Acupoints such as Lieque for Head & Neck (C5 dermatome of arm; C1-C5 form cervical plexus innervating neck and occipital area), Zhigou for Rib & Lat Chest (C7 dermatome of arm; C5-T1 form brachial plexus innervating lateral chest, back, and upper arms), Zusanli for Abdomen (Stomach meridian L3 dermatome of leg; T12-L4 form lumbar plexus innervating abdominal organs), Gongsun for Pregnancy (Spleen meridian L4 dermatome of leg), Sanyinjiao (L4-L5 dermatome boundary of leg). L4-S4 form sacral plexus innervating pelvic organs. Besides, Hegu for face and mouth (C6 dermatome of hands) is because facial pain will input to spinal trigeminal nucleus which could extend to C2/C3 with deviating fiber in C6 (lowest limit). Finally, Ashi point means that we can perform acupuncture on the pain point to trigger sharp sting pain for inhibiting/competing chronic pain and inflammation. Although there are six meridians in the arms, there are only five dermatomes in the arms (inner arm: C5 T1 C8 and outer arm: C6 C7 C8, both from radial to ulnar side). The ulnar inner arm is called heart meridian and the ulnar outer arm is called small intestine meridian. It is said that heart meridian and small intestine meridian are internal and external. Internal meridian can be treated by external meridian, vice versa. So the two should belong to the same dermatome: C8.

The second important mechanism of acupuncture is that it can up-regulate POMC production from skin cells (epithelium) and nerve cells (Zhang, Wang et al. 1996, Ji, Hu et al. 2013). The neuropeptide POMC can form ACTH, endorphin, MSH, and lipotropin (Nappi, Facchinetti et al. 1982, Yu, Zeng et al. 2013). ACTH can then

up-regulate glucocorticoid(Malizia, Andreucci et al. 1979). Endorphin can cause euphoria sensation and suppress pain and discomfort via inhibiting substance P(Cheng and Pomeranz 1979, Clement-Jones, McLoughlin et al. 1980, Facchinetti, Nappi et al. 1981, Stein 1995, Lee, Lee et al. 2009, Cheng, Yi et al. 2011, Zhang, Lao et al. 2014). Glucocorticoid can suppress inflammation which contributes to chronic pain(Bossut, Leshin et al. 1983, Zhang, Zhang et al. 2004, Zhang, Lao et al. 2005, Zhang, Wang et al. 2005, Li, Lao et al. 2008). MSH can suppress appetite/inflammation and lipotropin can cause lipolysis those are the mechanism for acupuncture caused body weight loss(Leonard, Kafoe et al. 1976, Brogden, Guthmiller et al. 2005, Fei, Tian de et al. 2011). ACTH can also stimulate epinephrine and norepinephrine to up-regulate sympathetic tones.(Kvorning and Akeson 2010) The up-regulated steroid, epinephrine, and norepinephrine is acute stress and pain response(Sun, Boney et al. 1985, Sugiyama, Xue et al. 1995). Acute stress can also elevate adenosine levels. The acute sharp pain is transmitted via A delta fiber compared to chronic pain and inflammation transmitted by C fiber. Both A delta fiber and C fiber belong to spinalthalamic tract, and they could compete with each other. Thus, the stimulation of acute stress/pain can suppress the chronic pain and inflammation. Epinephrine and norepinephrine can also aid to suppress inflammation. Thus, acupuncture can mediate its action via suppressing immunity.(Mori, Nishijo et al. 2002) Thus, acupuncture can treat allergic and autoimmune diseases such as allergic rhinitis. In addition, cold sensation is also transmitted via A delta fibers. The hot sensation via C fiber is also competing the cold sensation via A delta fiber. Thus, cold sensation produced by certain menthol oil can reduce the local heat, pain, and inflammation. Acupuncture can also reduce fever by this mechanism(Son, Park et al. 2002). Another mechanism is acupuncture can inhibit pain descending pathway by up-regulating serotonin. There are evidences showing that serotonin concentration is enhanced after electric acupuncture.(Chang, Tsai et al. 2004, Chang, Tsai et al. 2005) Serotonin and POMC also have positive interaction.(Taleisnik, Celis et al. 1974, Tiligada and Wilson 1989, Tsai, Lin et al. 1989, Jorgensen, Knigge et al. 2002, Jorgensen 2007, Zhang, Li et al. 2011, Zhang, Zhang et al. 2012, Doslikova, Garfield et al. 2013) The analgesic effects of acupuncture can be viewed by functional MRI in hypothalamus area, the key control area of autonomic system.(Cho, Chung et al. 1998, Chiu, Chung et al. 2003) This is so called acupuncture treats strong/hot/Yang syndrome.

The third mechanism of acupuncture is via nerve plasticity. Acupuncture can also be used to treat limb paralysis in stroke and cerebral palsy patients. The mechanism is not via anti-inflammation or analgesics. It is due to stimulation of nerve plasticity.

Nerve plasticity is the underlying principle of rehabilitation. If we continue to stimulate paralyzed limbs, we will be able to restore the sensory-brain cortex-motor circuit which is damaged in diseases such as stroke or cerebral palsy. Physical therapy or occupation therapy is to stimulate limb or face activity to restore their functions. Acupuncture via stimulating peripheral sensory and motor nerves can also promote nerve plasticity to aid the restore of the sensory-brain cortex-motor circuit. Repetitive stimulation via rehabilitation with acupuncture in injured peripheral limbs can help to re-build the circuit specifically. Besides, acupuncture can stimulate NGF production to cause synapse formation and neuron genesis. This may be the reason of nerve plasticity. This is the third mechanism of acupuncture. (Liu 2004, Sun, Xue et al. 2012)

From the second mechanism of acupuncture, we know the relationship between sympathetic system and needle stimulation. Actually, the useful clinical shu acupoints are located near the sympathetic ganglion. For example: Feishu:T3 Xinshu:T5 Ganshu:T9 Danshu:T10 Pishu:T11 Weishu:T12 Shenshu:L2 Dachangshu:L4 Xiaochangshu:S1 Panguanshu:S2. By stimulating these positions, we can affect the specific inner organs innervated by these specific sympathetic ganglions. This further explains the sympathetic mechanism of acupuncture.

Here, I will explain the mechanism of ear acupuncture. The inner ear cochlea is innervated by vagus nerves. Vagus nerve is the main parasympathetic nerve innervating majority of visceral organs in chest, abdomen, and pelvis. Thus, if we use ear acupuncture, vagal parasympathetic tone will be triggered (Choy, Tso et al. 1978, He, Wang et al. 2012). It can help to heart palpitation, weight control, anxiety/addiction, and insomnia via parasympathetic tone. (Cabioglu, Ergene et al. 2007)

The mechanism of tongue acupuncture can also be explained. The sensory nerve innervations for special sensory of tongue are the following: 1. Anterior 2/3 is facial nerve (chorda tympani) 2. Posterior 1/3 is glossopharyngeal nerve 3. Other is vagus nerve. Besides, anterior 2/3 is also innervated by lingual nerve (CN V) for general sensory. Then, the three nerves will go together in the solitary tract and then finally input to solitary nucleus. Solitary nucleus includes vagus nerve (parasympathetic nerve) from all chest, abdomen, and pelvic inner organs. Based on the above theory (competition-facilitation theory), the three nerve fibers in the solitary tract can inhibit each other. Thus, the tongue acupuncture by stimulating facial nerve & glossopharyngeal nerve can inhibit the vagus nerve sensory input from inner organs.

Thus, on the contrary to ear acupuncture, tongue acupuncture can inhibit parasympathetic nerve. Thus, it can treat swallowing pain, nausea/vomiting, chronic bronchiolitis, angina pectoris, menstruation pain, or chronic laryngitis/pharyngitis. Besides, nerve plasticity also plays an important role in tongue acupuncture. (Liu 2004, Streitberger, Ezzo et al. 2006) By this mechanism, it can help the dysarthria, dysphagia, or facial palsy of stroke patients (Yi, Tsai et al. 2004).

#### Mechanism of moxibustion

Moxibustion is just the opposite of acupuncture. Acupuncture is for strong syndrome and moxibustion is for weak syndrome. If acupuncture is not useful for one illness, then moxibustion is useful for this illness. Moxibustion is to produce local heat via meridians & acupoints. Heat sensation is transmitted via C fiber. C fiber is mediating heat, chronic pain, and inflammation. Heat will generate fever and up-regulate heat shock proteins (Lin, Chiu et al. 2001). Fever can stimulate host immune response. And, heat shock proteins can serve as danger signals to trigger immunity via binding Toll-like receptors and serving as antigen chaperons. Heat can also increase host metabolic rate to combat outside pathogen infection. Thus, moxibustion can up-regulate host immunity. (Yamashita, Ichiman et al. 2001) When a child is frequently undergoing URI or other infections, moxibustion can be used to promote host immune response against outside pathogens. Moxibustion is used during host hypo-immunity. Thus, moxibustion is for weak/cold/ying syndrome. Acupuncture facilitates A delta fiber competing C fiber, and moxibustion facilitates C fiber competing A delta fiber. This is the mechanism of acupuncture and moxibustion. I call this facilitation-competition theory.

#### The mechanism of message

Message is also used to relieve pain and inflammation. This can be explained by gate-control theory. The light touch or pressure sensation is transmitted via A beta fibers. The A beta fibers can also compete A delta or C fibers which transmitted acute pain and chronic pain, respectively. Thus, message (light touch and pressure) via A beta fiber can also suppress the pain and inflammation. However, since A beta fiber is not belonging to spinalthalamic tract, there is no direct contact inhibition like the competition between A delta fiber and C fiber. Thus, the message via A beta fiber is less effective than acupuncture or moxibustion. The mechanism of cupping & tui-na is similar to message.

## The mechanism of gua-sha & bloodletting

The mechanism of gua-sha & bloodletting is to trigger bleeding reaction (micro or macro-bleeding). Acute bleeding reaction is an acute stress response. The acute blood loss will up-regulate catecholamine (epinephrine and norepinephrine), corticosteroid, vasopressin, and ACTH. Thus, it is similar to acupuncture which can treat inflammatory disease and chronic pain. However, acute bleeding has its risk for blood loss and infection. Besides, gua-sha cannot specifically stimulate certain dermatome and certain A delta fibers competing C fibers. Gua-sha may also trigger C fiber activation. Thus, it cannot be as useful as acupuncture.

## Conclusion

The modern clinical medicine is very useful. However, it suffers from difficulties in managing chronic pain and inflammation. For examples: chronic low back pain and chronic allergic rhinitis are two troublesome cases not easily controlled by modern medicine. The traditional Chinese medicine such as acupuncture can help to manage these chronic pain and inflammation. In addition, moxibustion can help to up-regulate host immunity during the invasion of pathogen infection. Thus, acupuncture and moxibustion could be very useful and simple complement treatments to modern clinical medicine.

## Reference:

- Bossut, D. F., L. S. Leshin, M. W. Stromberg and P. V. Malven (1983). "Plasma cortisol and beta-endorphin in horses subjected to electro-acupuncture for cutaneous analgesia." Peptides **4**(4): 501-507.
- Brogden, K. A., J. M. Guthmiller, M. Salzet and M. Zasloff (2005). "The nervous system and innate immunity: the neuropeptide connection." Nat Immunol **6**(6): 558-564.
- Cabioglu, M. T., N. Ergene and U. Tan (2007). "Smoking cessation after acupuncture treatment." Int J Neurosci **117**(5): 571-578.
- Chang, F. C., H. Y. Tsai, M. C. Yu, P. L. Yi and J. G. Lin (2004). "The central serotonergic system mediates the analgesic effect of electroacupuncture on ZUSANLI (ST36) acupoints." J Biomed Sci **11**(2): 179-185.
- Chang, S. L., C. C. Tsai, J. G. Lin, C. L. Hsieh, R. T. Lin and J. T. Cheng (2005). "Involvement of serotonin in the hypoglycemic response to 2 Hz electroacupuncture of zusanli acupoint (ST36) in rats." Neurosci Lett **379**(1): 69-73.
- Chapple, W. (2013). "Proposed catalog of the neuroanatomy and the stratified

anatomy for the 361 acupuncture points of 14 channels." J Acupunct Meridian Stud **6**(5): 270-274.

Cheng, C. H., P. L. Yi, J. G. Lin and F. C. Chang (2011). "Endogenous opiates in the nucleus tractus solitarius mediate electroacupuncture-induced sleep activities in rats." Evid Based Complement Alternat Med **2011**: 159209.

Cheng, R. S. and B. Pomeranz (1979). "Electroacupuncture analgesia could be mediated by at least two pain-relieving mechanisms; endorphin and non-endorphin systems." Life Sci **25**(23): 1957-1962.

Chiu, J. H., M. S. Chung, H. C. Cheng, T. C. Yeh, J. C. Hsieh, C. Y. Chang, W. Y. Kuo, H. Cheng and L. T. Ho (2003). "Different central manifestations in response to electroacupuncture at analgesic and nonanalgesic acupoints in rats: a manganese-enhanced functional magnetic resonance imaging study." Can J Vet Res **67**(2): 94-101.

Cho, Z. H., S. C. Chung, J. P. Jones, J. B. Park, H. J. Park, H. J. Lee, E. K. Wong and B. I. Min (1998). "New findings of the correlation between acupoints and corresponding brain cortices using functional MRI." Proc Natl Acad Sci U S A **95**(5): 2670-2673.

Choy, Y. M., W. W. Tso, K. P. Fung, K. C. Leung, Y. F. Tsang, C. Y. Lee and D. Tsang (1978). "Suppression of narcotic withdrawals and plasma ACTH by auricular electroacupuncture." Biochem Biophys Res Commun **82**(1): 305-309.

Clement-Jones, V., L. McLoughlin, S. Tomlin, G. M. Besser, L. H. Rees and H. L. Wen (1980). "Increased beta-endorphin but not met-enkephalin levels in human cerebrospinal fluid after acupuncture for recurrent pain." Lancet **2**(8201): 946-949.

Doslikova, B., A. S. Garfield, J. Shaw, M. L. Evans, D. Burdakov, B. Billups and L. K. Heisler (2013). "5-HT<sub>2C</sub> receptor agonist anorectic efficacy potentiated by 5-HT<sub>1B</sub> receptor agonist coapplication: an effect mediated via increased proportion of pro-opiomelanocortin neurons activated." J Neurosci **33**(23): 9800-9804.

Facchinetti, F., G. Nappi, F. Savoldi and A. R. Genazzani (1981). "Primary headaches: reduced circulating beta-lipotropin and beta-endorphin levels with impaired reactivity to acupuncture." Cephalalgia **1**(4): 195-201.

Fei, W., R. Tian de, P. Tso and J. S. Han (2011). "Arcuate nucleus of hypothalamus is involved in mediating the satiety effect of electroacupuncture in obese rats." Peptides **32**(12): 2394-2399.

He, W., X. Wang, H. Shi, H. Shang, L. Li, X. Jing and B. Zhu (2012). "Auricular acupuncture and vagal regulation." Evid Based Complement Alternat Med **2012**: 786839.

Ji, B., J. Hu and S. Ma (2013). "Effects of electroacupuncture Zusanli (ST36) on food intake and expression of POMC and TRPV1 through afferents-medulla pathway in obese prone rats." Peptides **40**: 188-194.

Jorgensen, H., U. Knigge, A. Kjaer, M. Moller and J. Warberg (2002). "Serotonergic stimulation of corticotropin-releasing hormone and pro-opiomelanocortin gene expression." J Neuroendocrinol **14**(10): 788-795.

Jorgensen, H. S. (2007). "Studies on the neuroendocrine role of serotonin." Dan Med Bull **54**(4): 266-288.

Kvorning, N. and J. Akesson (2010). "Plasma adrenaline increases in anesthetized patients given electro-acupuncture before surgery." Pain Med **11**(7): 1126-1131.

Lee, H. J., J. H. Lee, E. O. Lee, K. H. Kim, S. H. Kim, K. S. Lee and H. J. Jung (2009). "Substance P and beta-endorphin mediate electro-acupuncture induced analgesia in mouse cancer pain model." J Exp Clin Cancer Res **28**: 102.

Leonard, B. E., W. F. Kafoe, A. J. Thody and S. Shuster (1976). "The effect of alpha-melanocyte stimulating hormone (alpha-msh) on the metabolism of biogenic amines in the rat brain." J Neurosci Res **2**(1): 39-45.

Li, A., L. Lao, Y. Wang, J. Xin, K. Ren, B. M. Berman, M. Tan and R. Zhang (2008). "Electroacupuncture activates corticotrophin-releasing hormone-containing neurons in the paraventricular nucleus of the hypothalamus to alleviate edema in a rat model of inflammation." BMC Complement Altern Med **8**: 20.

Lin, Y. H., J. H. Chiu, H. H. Tung, M. T. Tsou, W. Y. Lui and C. W. Wu (2001). "Preconditioning somatothermal stimulation on right seventh intercostal nerve territory increases hepatic heat shock protein 70 and protects the liver from ischemia-reperfusion injury in rats." J Surg Res **99**(2): 328-334.

Liu, Y. (2004). "Treatment of pseudobulbar paralysis by scalp acupuncture and sublingual needling." J Tradit Chin Med **24**(1): 26-27.

Malizia, E., G. Andreucci, D. Paolucci, F. Crescenzi, A. Fabbri and F. Fraioli (1979). "Electroacupuncture and peripheral beta-endorphin and ACTH levels." Lancet **2**(8141): 535-536.

Mori, H., K. Nishijo, H. Kawamura and T. Abo (2002). "Unique immunomodulation by electro-acupuncture in humans possibly via stimulation of the autonomic nervous system." Neurosci Lett **320**(1-2): 21-24.

Nappi, G., F. Facchinetti, G. Legnante, D. Parrini, F. Petraglia, F. Savoldi and A. R. Genazzani (1982). "Different releasing effects of traditional manual acupuncture and electro-acupuncture on proopiocortin-related peptides." Acupunct Electrother Res **7**(2-3): 93-103.

Sanchez-Araujo, M., A. J. Luckert-Barela, N. Sanchez, J. Torres and J. E. Conde (2014). "On dermatomes, meridians and points: results of a quasiexperimental study." Acupunct Med **32**(1): 62-69.

Son, Y. S., H. J. Park, O. B. Kwon, S. C. Jung, H. C. Shin and S. Lim (2002). "Antipyretic effects of acupuncture on the lipopolysaccharide-induced fever and expression of

interleukin-6 and interleukin-1 beta mRNAs in the hypothalamus of rats." Neurosci Lett **319**(1): 45-48.

Stein, C. (1995). "The control of pain in peripheral tissue by opioids." N Engl J Med **332**(25): 1685-1690.

Streitberger, K., J. Ezzo and A. Schneider (2006). "Acupuncture for nausea and vomiting: an update of clinical and experimental studies." Auton Neurosci **129**(1-2): 107-117.

Sugiyama, Y., Y. X. Xue and T. Mano (1995). "Transient increase in human muscle sympathetic nerve activity during manual acupuncture." Jpn J Physiol **45**(2): 337-345.

Sun, A. Y., F. Boney and D. Z. Lee (1985). "Electroacupuncture alters catecholamines in brain regions of rats." Neurochem Res **10**(2): 251-258.

Sun, Y., S. A. Xue and Z. Zuo (2012). "Acupuncture therapy on apoplectic aphasia rehabilitation." J Tradit Chin Med **32**(3): 314-321.

Taleisnik, S., M. E. Celis and M. E. Tomatis (1974). "Release of melanocyte-stimulating hormone by several stimuli through the activation of a 5-hydroxytryptamine-mediated inhibitory neuronal mechanism." Neuroendocrinology **13**(6): 327-338.

Tiligada, E. and J. F. Wilson (1989). "Regulation of alpha-melanocyte-stimulating hormone release from superfused slices of rat hypothalamus by serotonin and the interaction of serotonin with the dopaminergic system inhibiting peptide release." Brain Res **503**(2): 225-228.

Tsai, H. Y., J. G. Lin and R. Inoki (1989). "Further evidence for possible analgesic mechanism of electroacupuncture: effects on neuropeptides and serotonergic neurons in rat spinal cord." Jpn J Pharmacol **49**(2): 181-185.

Yamashita, H., Y. Ichiman and Y. Tanno (2001). "Changes in peripheral lymphocyte subpopulations after direct moxibustion." Am J Chin Med **29**(2): 227-235.

Yi, P. L., C. H. Tsai, J. G. Lin, H. J. Liu and F. C. Chang (2004). "Effects of electroacupuncture at 'Anmian (Extra)' acupoints on sleep activities in rats: the implication of the caudal nucleus tractus solitarius." J Biomed Sci **11**(5): 579-590.

Yu, J. S., B. Y. Zeng and C. L. Hsieh (2013). "Acupuncture stimulation and neuroendocrine regulation." Int Rev Neurobiol **111**: 125-140.

Zhang, J., M. Wang and L. He (1996). "Coexistence of Fos protein and proopiomelanocortin mRNA in hypothalamic arcuate nucleus following electroacupuncture." Acupunct Electrother Res **21**(1): 1-5.

Zhang, R., L. Lao, K. Ren and B. M. Berman (2014). "Mechanisms of acupuncture-electroacupuncture on persistent pain." Anesthesiology **120**(2): 482-503.

Zhang, R. X., L. Lao, X. Wang, A. Fan, L. Wang, K. Ren and B. M. Berman (2005).

"Electroacupuncture attenuates inflammation in a rat model." J Altern Complement Med **11**(1): 135-142.

Zhang, R. X., L. Wang, B. Liu, J. T. Qiao, K. Ren, B. M. Berman and L. Lao (2005). "Mu opioid receptor-containing neurons mediate electroacupuncture-produced anti-hyperalgesia in rats with hind paw inflammation." Brain Res **1048**(1-2): 235-240.

Zhang, S. P., J. S. Zhang, K. K. Yung and H. Q. Zhang (2004). "Non-opioid-dependent anti-inflammatory effects of low frequency electroacupuncture." Brain Res Bull **62**(4): 327-334.

Zhang, Y., A. Li, J. Xin, L. Lao, K. Ren, B. M. Berman, M. Tan and R. X. Zhang (2011). "Involvement of spinal serotonin receptors in electroacupuncture anti-hyperalgesia in an inflammatory pain rat model." Neurochem Res **36**(10): 1785-1792.

Zhang, Y., R. X. Zhang, M. Zhang, X. Y. Shen, A. Li, J. Xin, K. Ren, B. M. Berman, M. Tan and L. Lao (2012). "Electroacupuncture inhibition of hyperalgesia in an inflammatory pain rat model: involvement of distinct spinal serotonin and norepinephrine receptor subtypes." Br J Anaesth **109**(2): 245-252.