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# Why acupuncture in pain treatment?

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**Abstract**

Acupuncture is one of the branches of Chinese Traditional Medicine dating back almost 5 000 years. The expansion of China's trade and business relations with other Asian countries brought about the spreading of acupuncture in 7th Century. Nowadays, acupuncture is an interdisciplinary clinical field of Medicine dealing with treatment, diagnostics and prevention of mainly functional disorders, algic, allergic and addictive conditions of various etiology, localization and intensity. It draws from the millennia of experience of Oriental Medicine as well as contemporary knowledge of morphology, physiology and neurophysiology. The acupuncture method is based on influencing the body functions in a precise way by controlled irritation of particular active meridian points using special needles, heat (moxibustion), pressure (acupressure), underpressure (cupping), electricity (electroacupuncture), light (laser therapy), ultrasound (sonopuncture), static or pulsating electromagnetic field (magnetic therapy) and solutions (pharmacopuncture).The use of acupuncture as a method of pain relief in Modern Western Medicine is based on a wide range of clinical trials, and there is no doubt that it has significant effect in the treatment of acute and chronic pain classification. The introduction of gate-control theory and endogenous opioids facilitated the recognition of acupuncture in pain treatment.

**Abbreviations:**

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| ACTH | - adrenocorticotrophic hormone |
| ARs | - A1 adenosine receptor |
| ATP | - Adenosine triphosphate |
| CCK 8 | - Cholecystokinin octapeptide |
| CNS | - The Central Nervous System |
| CSF perfusate | - cerebrospinal fluid as perfusate |
| DNIC | - The diffuse noxious inhibitory controls |
| EA stimulation | - Electroacupuncture stimulation |
| EBM | - Evidence based Medicine |
| GABA | - gamma-aminobutyric acid |
| TENS | - transcutaneous electrical nerve stimulation |
| TCM | - Traditional Chinese Medicine |

REVIEW ARTICLE

## INTRODUCTION

Acupuncture is one of the branches of Chinese traditional Medicine dating back almost 5000 years. The expansion of China's trade and business relations with other Asian countries brought about the spreading of acupuncture first to Japan in the 7th Century, later also to Vietnam, India, Korea and Mongolia. In the 13th Century the first reports of acupuncture reached Europe, where it started to develop in the early 19th Century in France and spread to Germany, Italy and other European countries (De Morant 1994). Acupuncture reached Slovakia (Czechoslovakia) in 1960s and underwent a long development, at first on empirical, later also on a scientific basis (Šmirala *et al.* 2005). The origins of acupuncture lie in China which basically means treatment by needling and heating (Daedman *et al.* 2007). The name acupuncture was created in 17th Century Europe from the Latin words acus (needle) and punctio (puncture). Nowadays, acupuncture is an interdisciplinary clinical field of Medicine dealing with treatments, diagnostics and prevention of mainly functional disorders, algic, allergic and addictive conditions of various etiology, localization and intensity. Traditional Chinese Medical describes that there are *meridians*, invisible channels of vital energy or life force called *Qi* (*ch'i*) in the human and also in the animals body. Beginning in the fingertip meridians run up to the brain and to the specific organs to balance *Yin*, *Yang* and Qi. It draws from the millennia of experience in Oriental Medicine as well as contemporary knowledge of morphology, physiology and neurophysiology. However, the most important source of knowledge is the clinical experience gained by practical usage (Zhang 2000). The acupuncture method is based on influencing the body functions in a precise way by controlled irritation of particular active points in a meridian using special needles, heat (moxibustion), pressure (acupressure), underpressure (vacuum therapy, cupping), electricity (electroacupuncture), light (laser therapy), ultrasound (sonopuncture), static or pulsating electromagnetic field (magnetic therapy) and solutions (chemopuncture, pharmacopuncture) (Campbell 1998). Modern Medicine aims to reduce or eliminate spontaneous pathological excitation, regulate internal organs and their functions, improve impaired motor functions, alleviate pain at various nervous system levels, induce sedation and immuno-stimulation, regulate mental states. Physiology of pain is the field where acupuncture is most widely applied and studied (Man 1974).

## PAIN AND ACUPUNCTURE

Acupuncture is commonly used in pain treatment in traditional Chinese Medicine (TCM). Research suggests that somatic sensory stimulation engaging various body mechanisms can have multiple effects that explain the results of this treatment in certain pain conditions. Particularly good results of treatment by acupuncture can be achieved in functional disorders (Napadow *et al.* 2007). A common feature in many of the methods used for pain relief is the activation of somatic afferent nerves; for example through transcutaneous electrical nerve stimulation (TENS), vibration stimulation and massage; receptors or nerve fibers excited in the stimulated tissue. Acupuncture by manual or electrical stimulation is effective at triggering nerve impulses (Schneider *et al.* 2007). According to TCM, the needle stimulation in the active acupuncture point needs to produce a specific feeling (called *Deq*i), which is experienced as numbness, heaviness, radiating paraesthesia, sensation of muscle pain. It is a sign of activation of the thin myelinated A-delta nerve fibers. Low-frequency electrical stimulation (electro acupuncture) of sufficient intensity causes muscle contraction while activating high-threshold and low-threshold mechano-receptors in muscles (Zhou *et al.* 1988). Particular significance is attributed to the group of receptors in skeletal muscle with a high-threshold for mechanical stimulation which are innervated with A-delta fibers and C-fibers (Melzack *et al.* 2006). These are physiologically activated by strong muscle contraction, which can be functionally excited by dynamic movements. (Davis 1973). Functional modulation, as well as therapeutic effects attributed to acupuncture, occur also during muscular exercise. It is possible to argue that acupuncture and physical exercise with repetitive muscle contractions similarly activate these receptors and afferent nerve fibers (Dickenson 1991). One of the main effects of acupuncture is the release of not only the endogenous opioids, beta-endorphins, enkephalins, dynorphins but also non-opioid compounds, such as serotonin, norepinephrine, GABA and oxytocin which seems to be essential for the induction of functional changes in various organs. NMDA receptors play a significant role as well. (Gaio *et al.* 2012). Studies in human volunteers and laboratory animals have shown that diffuse noxious inhibitory controls (DNIC) may be involved in the mechanisms of acupuncture. DNIC are part of the biological pain control system (Carlsson 2002; Schliessbach *et al.* 2012). Endogenous opioids have been identified and proved to have an affinity for a variety of opioid receptors. Particular attention was paid to beta-endorphins which have a high affinity for μ-receptors and represent a vital factor in pain control (van Wijk & Veldedhuijzen 2010).

Endogenous opioid beta-endorphin is released by two different systems – neural network and blood. The first system includes the hypothalamus and the neural network leading to the midbrain and brainstem and in this way can affect pain sensitivity as well as autonomous functions. There is evidence that the hypothalamus nuclei play a vital role in the mediating effect of acupuncture (Treister *et al.* 2010). Damage in the arcuate nucleus eliminates the analgesic effect of low-frequency but not of high-frequency electro-acupuncture.

Low-frequency electrical stimulation induced circulatory changes in multiple tissues (Zhu 1981; Hsieh *et al.* 2001). Increase in the beta-endorphin levels was observed in the animal brain tissue both after acupuncture treatment and muscular exercise. Although the details are still unknown, experimental and clinical evidence indicates that acupuncture can also affect the sympathetic nervous system on the hypothalamus-hypophysis level (Guo *et al.* 2004).

The second system includes the release of the beta-endorphin levels into blood. Proopiomelanocortin in the hypophysis produces the equimolar amount of beta-endorphin and ACTH after muscular exercise and also after acupuncture treatment and its modifications in the active acupuncture point (Li *et al.* 2008). These agents affect various target organs. The two beta-endorphin systems may work independently, but both can be stimulated by afferent nervous activity. It was found that stress can cause increased concentrations of beta-endorphin and ACTH levels in blood, regardless of their increase in the brain (Rokyta *et al.* 2006). Since the blood-brain barrier is relatively impermeable to the circulating peptides, the concentration of beta-endorphin in plasma may not be relevant to the opioid receptors in the brain. The effects of endorphins are important because endorphins are secreted during both the acupuncture and muscular exercise and may induce changes similar to the effects of morphine agonist and naloxone, which is a non-specific antagonist of beta-endorphins (Mann *et al.* 2005).

The effects of both energetic muscular exercise and the afferent neural stimulation fall into two phases. First, there is the excitation of the sympathetic nervous system with increased heartbeat and the regional vasoconstriction with elevated blood pressure resulting in more efficient muscle perfusion, while the blood flow in multiple internal organs and in the skin can be reduced. These activities enable adaptation to muscle workload provided that the stimulation of the muscle receptors by muscular exercise or acupuncture needles continues for a sufficient time, while releasing endogenous opioids (Mark 1973)

In the 1970s and 1980s a large experimental research by a group of Chinese scientists in Beijing demonstrated that the cerebrospinal fluid collected from rabbits after acupuncture analgesia also induced analgesia when applied to the fourth brain chamber of other rabbits. This proved the humoral basis of the analgesic effect of acupuncture, although the nature of the substance was unknown at that time. Later on, a group of Toronto scientists led by Pomeranz and Chiu (1976) Mendelson (1977) and Ehrenpreis (1985) established the analgesic effect of acupuncture via endogenous opioids (Lundeberg and Steiner-Victorin 2002). The importance of the periaqueductal gray in the nociception is well known and various clinical trials pointed to electrostimulation analgesia in cases of chronic pain where levels of endorphins in cerebrospinal fluid are high and may be suppressed by naloxone. It was also found that the long-term stimulation also weakened the analgesic effect and the increase in endogenous opioids. This was resolved by administration of the L-tryptophan amino acid a precursor of the serotonin biosynthesis in the CNS (Martuliak 2014). The connection between serotonin and pain regulation is significant; the stimulation of the periaqueductal gray leads to the activation of the descending inhibitory serotonergic system, which is linked to the raphe nuclei in the brain stem. The descending inhibitory track (tractus reticulospinalis) is involved in the regulation of pain threshold to nociceptive impulse at the substantia gelatinosa posterior horn level of spinal cord (Wu *et al.* 2002).

Studies of Swedish Pharmacologists found that in chronic pain the concentration of endorphins in the spinal fluid is markedly reduced (Carlsson 2002). Cholecystokinin octapeptide (CCK 8) has been shown to function in the CNS as a neuropeptide with potent antiopioid activity (Lee *et al.* 2003). It hinders opioid analgesia and facilitates opioid tolerance. Studies of authors (Ulett *et al.* 1998; Zhou *et al.* 1988; Hammes *et al.* 2002) and many others have found that electroacupuncture stimulation caused a substantial increase of immunoreactivity in CSF perfusate of the rat spinal cord. It was found that CCK 8 is in fact increasingly released at frequencies from 100 Hz to 15 Hz (Han *et al.* 1985). Opioid peptides are activated and CCK 8 is not produced at low frequencies 1–2 Hz. Since the CCK 8 was found to have potent antiopioid activity at the spinal level, it would be expected to reduce the electroacupuncture analgesia which is opioid-mediated. The lack of acupuncture effectiveness may be attributed to the high levels of cholecystokinin opioid antagonist in the brain (Rokyta *et al.* 2015). This known effect of the endogenous opioids is produced by EA stimulation and may be hindered by naloxone in laboratory animals as well as in humans. It does not apply unequivocally since the low frequency EA stimulation activates opioid peptides derived from propio-enkephalins while the high frequency of 100 Hz activates the proprio-dynorphin group (Ulett *et al.* 1998; Han 2003).

Recent research suggests that there is another category of pain besides the nociceptive and neurogenic pain (Kalso *et al.* 1999). Exposure to chemical compounds and infectious agents and consequent major changes transform the pain and bring about increased sensitivity, described as chronic pain syndrome (Lundeberg & Steiner-Victorin 2002). In clinical trials, acupuncture needle stimulation or low frequency electroacupuncture were effective only in certain nociceptive states, but the high frequency stimulation proves more effective in comparison with manual acupuncture. The use of needles is usually ineffective in patients with chronic pain syndrome and high anxiety. It was also found that patients respond to acupuncture treatment better when they are not under stress (Rokyta *et al.* 2015).

The results of some clinical trials in human volunteers and in laboratory animals provide evidence of the involvement of the nervous and endocrine system in acupuncture. These studies have found that acupuncture induces a variety of biological responses, which occur both locally as well as in a remote location (off-center). Studies on the stress response in animal models showed several outcomes of acupuncture techniques: Acupuncture was able to reduce the concentration of noradrenaline in the brain and in the blood circulation, it reduced the production of epinephrine in animals exposed to restraint stress; it also induced long-term behavioral and cardiovascular depression and anxiolytic effects commonly observed in animals in captivity. Physical and psychological stressors may cause various behavioral and biochemical changes in the body, including effects on cardiac function, blood pressure, and systemic release of catecholamines. Forced restraint has shown to be a simple physiological stressor that causes significant increase of heart activity, blood pressure and levels of norepinephrine and epinephrine, activation of the sympatico-adrenal system and the hypothalamic-pituitary axis (Zeng *et al.* 2013).

Another possibility how to alleviate pain is the A 1 adenosine receptor (Zylka 2010). There are four types of adenosine receptors, which all belong to the G protein-binding group and are located in the whole body. Therefore, they participate in most of physiological as well as pathological processes (Goldman *et al.* 2010). Adenosine is produced by the degradation of adenosine triphosphate (ATP), it reacts to mechanical and chemical stimuli and it binds to adenosine receptors (Trincavelli *et al.* 2010). Pain is suppressed upon the binding of adenosine to the A1 receptor. This would suggest that the A1 receptor agonists have analgetic effect (Takano *et al.* 2012).

## CONCLUSION

Even though recently there has been a significant development in the acupuncture research many challenges still remain in place for future research efforts. One of them is the fact that Eastern Medicine is based on syndrome differentiation and individual approach. Blind and standardized controlled trials in EBM are therefore problematic in acupuncture practice (Hegyi 2015). The risk of blinding bias is assessed as low in most controlled studies despite the fact that the Acupuncturists know if they are performing sham or real acupuncture which poses a certain risk of unblinding. However, this problem is common to all non-pharmaco-logical treatment trials (physical therapy, cognitive therapies not using placebo control) (Endress *et al.* 2007).

The use of different controls in clinical trials (for example sham, no or minimal acupuncture) made the trials more complicated and hindered the researchers from proving the effect of acupuncture (Hammes *et al.* 2002; Haake *et al.* 2007). Integration of all these factors in acupuncture research is the greatest challenge for the researchers. Therefore, the unification of standards and evaluation indexes would be a logical next step in acupuncture research.

While basic research done primarily on animals or healthy human subjects showed highly positive physiological effects of acupuncture the results of clinical trials are a lot less optimistic even minimal. Current knowledge suggests that animal subjects used for mechanical acupuncture trials are not sufficient for assessing the vital elements of acupuncture treatment such as Qi, meridians and acupuncture points. Thus, it is necessary to find more suitable animal subjects to demonstrate these elements (Okada & Kawakita 2009). Considerable evidence supports the hypothesis that acupuncture is superior to usual care. In research trials, however, acupuncture is only slightly more effective than sham acupuncture; and sham, in turn, shows higher effect in comparison to no treatment control group than other placebo controls (Endress *et al.* 2007).

This would suggest that acupuncture is a kind of placebo treatment based on random skin needling. Nevertheless, acupuncture is a comprehensive therapy including the placebo effect, non-specific physiological effects of needling and specific effects. Translational Medicine facilitating the cooperation of theoretical research and clinical practice should aim to merge laboratory techniques with clinical trial results. The effect of acupuncture involves many factors, such as depth, frequency, angle and movement during needling. Acupuncture might possibly affect the biomarkers in laboratory trials. All these factors together could help us understand the interconnection between the needling properties, changes in biological markers and clinical results (King *et al.* 2009).

When evaluating the therapy efficacy stronger emphasis should be put on the effect and cost effectiveness of acupuncture with regard to the health insurance system. Acupuncture's capacity to provide available healthcare to millions of people in various living conditions is a significant factor in the evaluation as well.

Acupuncture has an ancient history, the research in this area dates back to the 19$^{th}$ Century and it is still on the rise nowadays. Scientists as well as medical practitioners strive to understand its physiological and psychological mechanisms and assess the real effect of acupuncture in clinical practice. Acupuncture was proved to be beneficial in treatment of a number of conditions. The basic mechanisms are now examined and interpreted by the means of modern science and technology (Ondrejkovičová *et al.* 2015).

There are many issues in acupuncture research, such as the underlying mechanisms of needling; specificity of acupoints; understanding how individual features of acupuncture transfer into physiological and clinical outcomes. All these issues need to be solved in order to maximize clinical benefits of acupuncture (Šmirala *et al.* 2005).

Acupuncture works with human internal chemistry, so even though it does not administer any external chemical agents, it achieves practical results. This approach has many advantages compared to treatment with pharmaceuticals. From the modern scientific point of view, acupuncture is a field of Medicine with highly developed methods of treatment, prevention and diagnostics. Extensive empirical and clinical experience and ongoing research continuously strengthen its scientific basis (Hrobjatsson & Gotzsche 2001). Acupuncture as a part of Traditional Chinese Medicine represents a unique gift in medical practitioner's hands. It is a gift of a perspective different from conventional Western modern thinking offering an holistic approach typical of Eastern civilizations. Inclusion of both ways of thinking in modern science might bring about a solution to vital questions of life and living systems (Šmirala *et al.* 2011).

REFERENCES


1 Carlsson C (2002). Acupuncture mechanisms for clinically relevant long-term effects – Reconsideration and hypothesis. Acupuncture in Medicine. **20**(2–3): 82–99.
2 Campbell A (1998). Methods of acupuncture. In. Filshie J, White. A medical Acupuncture – A Western Scientific. Approach.Edinburg: Churchill Livingstone, p. 19–32.
3 Daedman PA, Al Khafaji M, Baker K (2007). A Manual of Acupuncture. East Sussex. China: J Chinese Medic. Publ. 312. ISBN 978-0-9510546-5-9.
4 Davis ME (1973). Acupuncture and physiotherapy – a decision for physiotherapists. Australian J Physiotherapy. **XVIV**: 5–8.
5 Dickenson AH (1991). Mechanizmus of the analgesis action of opioids. British Medical Bulletin. **47**: 690–702.
6 De Morant GS (1994). Chinese Acupuncture [on line]. Paris: Paradigm Publ. ISBN 9780912.111.3, 896. [cit. 2016.03.24].
7 Ehrenpreis S (1985). Analgesic Properties and Enkephalinase Inhibitors: Animal and Human Studies. Prog. Clin. Biol. Res. **192**: 363–370.
8 Endres HG, Böwing G, Diener HC, Lange S, Maier C, Molsberger A, Zenz M, Vickers AJ, Tegenthoff M (2007). Acupuncture for tension-type headache: a multicentre, sham-controlled, patient- and observer-blinded, randomised trial. J Headache Pain. **8**(5): 306–314.
9 Goldman N, Chen M, Fujita T, Xu Q, Peng W, Liu W, *et al.* (2010). Adenosine A1 receptors mediate local anti-nociceptive effects of acupuncture. Nat Neurosci. **13**(7): 883–8.
10 Gaio X, Qiao Y, Jia B, Jing X, Cheng B, Wen L *et al.* ( 2012). NMDA Receptor-Dependent Synaptic Activity in Dorsal Motor Nucleus of Vagus Mediates the Enhancement of Gastric Motility by Stimulating ST 36. Evidence-Based Complementary and Alternative Medicine. **2012**: Article ID 438460, 11 p.
11 Guo J, Gao H, Chen J, Zhao P, Cao X, Li Y *et al.* (2004). Modulation of the gene expression in the protective effects of electroacupuncture against cerebral ischemia: A cDNA microarray study in Acupuncture. In Electro-Therapeutics Research. **29**(3–4): 173.
12 Haake M, Müller HH, Schade-Brittinger C, Basler HD, Schäfer H, Maier C, Endres HG, Trampisch HJ, Molsberger A (2007). German Acupuncture Trials (GERAC) for chronic low back pain: randomized, multicenter, blinded, parallel-group trial with 3 groups. Arch Intern Med. **167**(17): 1892–1898. Erratum in: Arch Intern Med. **167**(19): 2072.
13 Hammes MG, Flatau B, Backer M, Ehringer S, Conrad B, Tolle TR (2002). Investigations on the effect of acupuncture on affective and sensory components of pain in patients with different stages of chronic pain. Schmerz. **16**(2): 103–113.
14 Han JS, Ding XZ, Fan SG (1985). Is cholecystokinin octapeptide (CCK-8) a candidate for endogenous antiopioid substate? Neuropeptides. **5**(4): 399–402.
15 Han JS (2003). Acupuncture: neuropeptide release produced by electrical stimulation of different frequencies. Trends Neurosci. **26**(1): 17–22.
16 Hegyi G (2015). Acupuncture, TCM as part of the EBM, in the current state of research: achievements, doubts, solutions. Health Academy. **6**(1): 22–36.
17 Hrobjatsson A, Gotzsche PC (2001). Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med. **344**(21): 1594–602.
18 Hsieh JC, Tu CH,Chen FP, Chen M, Yeh TC, Cheng HC *et al.* ( 2001). Activation of the hypothalamus charakterizes the acupuncture stimulation at the analgetic point in human: A position emission tomography study. Neuroscience Letters. **307**(2): 105–108.
19 Kalso E, Mc Quay HJ, Wiesenfeld-Hallin Z (1999). Opioid Sensitivity of Chronic Noncancer Pain. Seattle: IASP Press. 14:397. ISBN 0-931092-28-0.
20 King CD, Wong F, Curriet T, Mauderli A, Fillingim RB, Rilley JL (2009). Deficiency in endogenous modulation of prolonged heat pain in patients with Irritable Bowel Syndrome and Temporomandibular Disorder. Pain **143**(3): 172–178.
21 Lee GS, Han JB, Shin MK, Hong MC,Kim SW, Min BI *et al.* (2003). Enhancement of electroacupuncture-induced analgetic effect in cholecystokinin A-receptor deficient rats. In: Brain Research Bulletin. **62**(2): 161
22 Li W, Cobbin D, Zaslawski C (2008). A comparison of effects on regional pressure pain threshold produced by deep needling of LI4 and LI11, individually and in combination. Complementary Therapies in Medicine. **16**(5): 278–287.
23 Lundeberg T, Steiner-Victoria E (2002). It's there a physiological basis for the use of acupuncture in pain? Intern Congress Series **1238**: 3–10.
24 Martuliak I (2014). Pain pathology in clinical practice. (Patológia bolesti pre klinickú prax.1st ed. Banská Bystrica: Dali-BB, 2014, p. 310.
25 Man P (1974). Acupuncture analgesia. Report of 100 experiments. British Journal Anaest. 46: 361–364.
26 Mann L, Lundeberg T, Holmang A, Aloe L (2005). Effect of electro-acupuncture on ovarian expression of alpha 1 and beta 2 adrenoreceptors, and p75 neurotrophin receptors in rats with steroid induced polycystic ovaries. Reproductive Biology and Endocrinology. **21**: 3.
27 Mark LC (1973). Double-blind studies of acupuncture. JAMA. **225**(12): 1532.
28 Melzack R, Bond R, Simoson HK (2006). Pain, its nature and treatment. Edinburgh Churchill Livingstone Elsevier, p. 309.
29 Mendelson G (1977). The possible role of enkephalin in the mechanism of acupuncture analgesia in man. Med Hypotheses. **3**(4): 144–5.
30 Napadow V, Liu J, Li M, Kettner N, Ryan A, Kwong KK, Hui KK, Audette JF (2007). Somatosensory cortical plasticity in carpal tunnel syndrome treated by acupuncture. Hum Brain Mapp. **28**(3): 159–171.
31 Okada K, Kawakita K (2009). Analgesic action of acupuncture and moxibustion: a review of unique approaches in Japan. eCAM. **6**(1): 11–17.
32 Ondrejkovičová A, Petrovics G, Hegyi G (2015). Biomedical Effects of Acupuncture. Int. Complement Alt Med. **2**(2): 1–5.
33 Pomeranz B, Chiu D (1976). Naloxone blockade of acupuncture analgesia: Endorphin implicated. Life Sci. **19**: 1757–1762.
34 Rokyta R, Krišiak M, Kozák J (2006). Pain. (Bolesť) 1. ed. Prague: Tigis. p. 664.
35 Rokyta R, Bernášková K, Franěk M. Pekárková I, Pometlová M, Matejovská I, Šlambertova *et al.* (2015). Physoplogy and Pathologic Physiology for Clinical Practice. (Fyziologie a patologická fyziologie pro klinickou praxi). Praha: Grada, p. 680.
36 Schneider A, Streitberger A, Joos S (2007). Acupuncture treatment in gastrointestinal diseases: a systematic review. World J. Gastroenterol. **13**(25): 3417–3424.

37 Schliessbach J, van der Klift E, Siegenthaler A, Arendt-Nielsen L, Curatolo M, Streitberger K (2012). Does acupuncture needling induce analgesic effects comparable to diffuse noxious inhibitory controls? Evid Based Complement Alternat Med. **2012**: 785613.
38 Šmirala J, Ondrejkovičová A, Petrovics G, Rosinský T, Šmirala J jr. (2005). A compendium of acupuncture 1 (Kompendium akupunktúry 1). 1st ed. Martin: Osveta, 2005, p. 447.
39 Šmirala J, Ondrejkovičová A, Petrovics G, Balogh V, Bangha O, Rosinský T *et al.* (2011). A compendium of acupuncture 2. (Kompendium akupunktúry 2). 1st ed. Martin: Osveta, 2011, p. 441.
40 Takano T, Chen X, Luo F, Fujita T, Ren Z, Goldman N, *et al.* (2012). Traditional acupuncture triggers a local increase in adenosine in human subjects. J Pain. **13**(12): 1215–1223.
41 Trincavelli ML, Daniele P, Martini C (2010). Adenosine receptors: what we know and what we are learning. Curr. Top Med. Chem. **10**(9): 860–877.
42 Treister R, Eisenbach E, Gershon E, Haddad M, Pud D (2010) Factors affecting – and relationships between – different modes of endogenous pain modulation in healthy volunteers. Eur J Pain **14**(6): 608–614.
43 Ulett GA, Han S, Han JS (1998). Electroacupuncture: Mechanisms and Clinical Application. Biol Psychiatry. **44**: 129–138.
44 Van Wijk D, Veldedhuijyen DS (2010). Perspective on diffuse noxious inhibitory controls as a model of endogenous pain modulation in clinical pain syndromes. J Pain. **11**(5): 408–419.
45 Wu MT, Sheen JM, Chuang KH, Yang P,Chin SL,Tsai CY *et al.* (2002). Neuronal specificity of acupuncture response: A fMRI study with electroacupuncture. NeuroImage. **16**: 1028–1937.
46 Zhang X (2000). General guidelines for methodologies on research and evaluation of traditional Medicine. Document of WHO Geneva, p. 137.
47 ZhouY, Han J, SunY, Shen J (1988). Increased release of immunoreactive CCK-8 by electroacupuncture and enhancement of electroacupuncture analgesia by CCK-8 Antagonist in rat spinal cord. Exp Neurol. **24**: 554–562.
48 Zeng BY, Zhao K, Liang FR (2013). Neurobiology of Acupuncture. Int Rev Neurobiol.111. Elsevier. ISSN 0074-7742.
49 Zhu Z (1981). Research Advances in electrical specificity of meridian and acupoint. Am J Acupunct. **9**: 203–205.
50 Zylka MJ (2010). Needling adenosine receptors for pain relief. Nature Neuroscience. **13**(7): 783–784.