



Acupuncture, autonomic nervous system and biophysical origin of acupuncture system

Akupunktura, autonomni nervni sistem i biofizičko poreklo akupunktornog sistema

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Introduction

Acupuncture (针刺, zhēncì) represents a therapeutic method of traditional Chinese medicine (TCM) that is based on stabbing needles in specific places on the skin called acupuncture points. They are located along meridians through which qì (气), vital force is running. Unity of dual principles yīn (阴, yīn) and yáng (阳, yáng) in organism is comprising qì and they are reflected in the form of periodic (night-cooling and day-rising*) Disturbance of qì flow TCM physicians consider as a cause of disease occurrence. They use acupuncture in purpose of lǐqì (理气), regulation and reparation of qì flow¹. For good therapeutic response it is necessary to find and insert needle in acupuncture point, point of qì (气穴, qìxué). Sign of insertion needle into acupuncture point (qìxué) is local sensation of specific pain, numbness, heaviness... It is called déqì (得气). In order to find acupuncture point (qìxué), TCM physicians use old Chinese maps of acupuncture system (AS). These Chinese maps of AS (经络, jīngluò) were established about 5,200 years ago². However, they are still scientifically unexplained. Last 4 decades numerous biomedical reports have not provided an agreement

about determination of physical structures of AS (jīngluò)³. There are several histological candidates: microtubules, gap junctions, clusters of water^{1, 4}, collagen fibers, fascia³, Bunghans channels (tread-like structures identified inside of the lymph channels)¹, nerves of central nervous system (CNS)⁵ and autonomic nervous system (ANS)⁶, etc. Due to impossibility of proving absolute physical or functional identity of AS (jīngluò) with any of these structures or with other organic systems, it is uncertain whether AS (jīngluò) and qì have anatomical analogons in classical medicine. Appropriate hypothetic biophysical model of AS (jīngluò) should give explanation of one seemingly simple phenomena: in which way inserting little and sharp needles (without injection of substance or radiation) is producing effective and fast clinical outcomes⁷. Characterization of biological structures of AS (jīngluò) would help in clarifying mechanisms of acupuncture and related techniques, as well as the development of new methods for diagnostics and therapy based on TCM principles. But, so far histological research has not identified structures that fit with anatomical locations of AS (jīngluò) presented in Chinese maps. It is possible that AS (jīngluò) is not made of physical structures, but from functional (physiological or signaling) interconnections that old Chinese were symbolically representing in form of anatomical paths (luò), the well-known acupuncture meridians. If that is so, than modeling physiological processes during therapeutic responses of acupuncture might be significant for indication on nature of AS (jīngluò). Bearing in mind that ANS is one of the most significant systems that regulates organic func-

* It is incoded in etymology of Chinese characters: character for yīn contain subcharacter 月 (yuè) which means moon and character for yáng contain subcharacter 日 (rì) which means sun.

tions⁸⁻¹⁵ it follows that characteristics of ANS exactly should be in focus of evaluation before and after acupuncture therapies. Therefore, it is first necessary to explore and summarize recent research about the influence of acupuncture on ANS. The research will speak firstly about the nature of AS (jīngluò) and significance of ANS for therapeutic effects of acupuncture^{3,6}.

Influence of acupuncture on autonomic nervous system

In the review article "Acupuncture and heart rate variability" Korean researchers, Lee et al.¹⁶ made an overview of articles from 14 databases, without restriction of year and language. Only 25 papers have passed their criteria of control randomized trials. They determinate that only 5 studies showed significant difference of effects of acupuncture on heart rate variability (HRV) in comparison with sham (placebo) acupuncture in control groups. They claim that these results are not consistent and methodologically comparable between each other. So, they conclude that (until their review research) there are no evidences that acupuncture produces significant effects on HRV, one regional sector of ANS. Since the ANS is regionally organized and regionally controlled, this report does not exclude that neural regulation of other organ systems than cardiovascular (i.e. cerebral blood flow, respiration, temperature regulation, muscle blood flow, alimentary function, renal function) is influenced by acupuncture^{17,18}.

Therefore, our theoretical analysis takes in consideration papers about influence of acupuncture on ANS published from 2010 to present. In order to approach them we have choose 3 most common used web services for biomedicine topics (Science Direct, PubMed and Medline). In browsers of it, words "acupuncture" and "autonomic nervous system" were typed. We found and analyzed total of 18 papers¹⁹⁻³⁷ that were directly related on this topic. Main inclusion criteria were use of manual acupuncture in human subjects because others involve various factors like biochemical or electromagnetic influence on different organism regulation mechanisms. Thus, research of electro acupuncture, laser acupuncture, moxibution, pharmacopuncture and research on animals were excluded. It is possible to derive several introducing remarks: in most papers evaluation of cardiovascular autonomic functions was obtained through time and frequency analysis of HRV; short term measuring procedures of parameters of autonomic regulation were usually performed (5, 10, 15, 30 min) before, during and after one acupuncture treatment. In all papers there is significant positive effect of acupuncture at least on one parameter of cardiovascular autonomic regulation. After these insights it is possible to extract several assumptions about biophysical base of acupuncture influence on ANS.

Hypotheses about influence of acupuncture on autonomic nervous system

In single research papers about influence of acupuncture on ANS^{6, 19-37} there are few detailed interpretations of

obtained results in context of explanation of mechanisms of acupuncture. Thus, generalization of these various research results can hardly be reduced to a single theory. While summarizing results from reviewed papers we generalized several hypotheses that might indicate on biophysical nature of AS (jīngluò). Those are: neural hypothesis, pain stimulus, placebo effect, mechanistic model and complementary model of ANS and AS (jīngluò).

Neural hypothesis

Despite of significant AS (jīngluò) and CNS relationships^{5,38}, correlation of changes in autonomic functions and electroencephalography (EEG) signals under the influence of acupuncture³⁹, there are no clear evidences of coincidence of AS (jīngluò) and the so called psycho-neuro-endocrine system⁴⁰. First of all, acupuncture points and meridians (qixuélù) within Chinese maps are not coinciding anatomically with nerves of CNS and ANS. That was pointed on in handbooks of Serbian acupuncturologists and biomedical engineers more than 30 years ago^{41,42}. Accidentally, certain acupuncture points could be found on places of neural pathways. Also, from the review of the literature^{6, 19-37} there are no direct confirmations that acupuncture effects are made only through neural mechanisms. It is certain, however, that ANS, under the influence of acupuncture, optimizes involuntary functions (for example pulse, blood pressure, contractions of smooth muscles of abdomen etc). These are efferent (motor) neural mechanisms. It is not clear which mechanism is in the basis of influence of acupuncture on ANS. From positive effect of acupuncture on cardiovascular diseases Mehta et al.³² assume that cardiovascular-specific acupuncture points are stimulating groups of III and IV afferent (sensor) autonomic neural pathways; through them neural signals are forwarded to regions in hypothalamus, midbrain and medulla that, afterwards, regulate cardiovascular system²⁹. Longhurst⁶ agrees with pointing on these sensor nerves in transferring acupuncture stimuli. Referring to objections that his hypothesis gave no explanation of clinically observable characteristics of AS (jīngluò)⁴³, Longhurst replays that while applying electroacupuncture on stomach meridian his team in Graz got results of change in sympathetic outflow that they assume to come from visceral region. This is possible because stimulated nerves are crossing in common interneural parts of medulla from which, primarily, regulation of cardiovascular system (CVS) is directed. Then, he claims that there are no evidences of existence of meridians in physical form. There are neural afferent pathways, i.e. from foot to spine that are longer than 1 meter. For laser acupuncture he claims that there are not enough publications in high quality journals⁴⁴. However, as it was mentioned, ANS is not anatomically identified with AS (jīngluò). His explanation of afferent mechanisms of acupuncture should be explored at least through correlation of parameters of functions that are regulated by ANS and parameters of neural activities of afferent autonomic nerves. Toma et al.²¹ determined in 14 subjects that acupuncture of LI4 acupuncture point in rest cause no effects on HRV and skin sympathetic neural activity (SSNA,

measured on peroneal nerve by means of intercellular electrodes); otherwise, during handgrip it gives results of lesser increase of SSNA than without acupuncture treatment. Authors of research assume that this result might be obtained because acupuncture decreases central sympathoexcitatoric effect on the skin that is usually mobilized by physical activities (exercise). Bearing in mind that LI4 is innervated by radial nerve, and that neurogram was recorded on common (peroneal) nerve, they conclude that effect of acupuncture in their experiment was systemic (non local). Yet, they admitted that detailed mechanism of their result is unknown. Anyway, if future research confirms their assumptions, several questions will still left without answers: how acupuncture affects nerves in cases when they are not coinciding with places of acupuncture points? Which kind of stimuli takes place: ordinary mechanical, biochemical or something else? How are achieved fast effects of acupuncture stimulations, and how are achieved long lasting therapeutic effects, especially in diseases that are not neural? Cheng³³ thinks that if acupuncture might produce signal to brain to secrete out endorphins, then it can produce signal for other neurotransmitters as well. Local effects of acupuncture on examples of muscle-skeletal disturbances, he interprets that comes from micro-damage of tissue, increased local blood circulation, mechanisms of regeneration and analgesia. Accordingly, acupuncture needles stimulate nerves in local tissue. However, ancient TCM physicians would hardly be satisfied with theoretical identifications of AS (jīngluò) and ANS. If the effects of acupuncture are reduced to neural mechanisms only, old Chinese concept of AS (jīngluò) becomes an abstract construction. In line with that, no research so far has obtained evidence for this. On the basis of the above results it is more certain that some structural-functional dependence exists between AS (jīngluò) and ANS.

Painful stimulus

In their research Kang et al.²⁰ determinate a statistically significant decrease of HRV and increase of skin conductance response (SCR), but without significant difference between real and sham acupuncture. Subjective feeling of pain with real acupuncture treatments was more correlated with SCR changes than with changes of HRV. In sham acupuncture (control group) there was no such correlation. Therefore, authors of research made a conclusion that acupuncture by itself does not produce real therapeutic effect. In their opinion, the therapeutic effect is more related with response of ANS on pain. Also, response of ANS during acupuncture stimulation is not necessarily reflecting subjective reaction on pain, but expecting painful stubbing as well. By means of correlation of magnetic resonance imaging (MRI) excitation of brain regions and HRV during acupuncture Beissner et al.²⁵ assumed that acupuncture might be specific pain stimulation. In that way pain from acupuncture might create analgesic effects and therapeutic potentials. It was concluded, from insight that stronger and more painful acupuncture stimulation was, greater decrease of heart rate was registered. Similar results were obtained by Bäcker et al.²⁷. They found that significant increase of electrodermal activity was greater

during more intensive acupuncture stimulation. Their explanation is that greater doses of acupuncture lead to higher pain in subjects. Then, this painful stimulus activates sympathetic ANS response and defending mechanisms. From this it could be assumed that AS (jīngluò) represents hypothetical paths through which painful stimulus is transferred to ANS. ANS reacts on pain, stress, fear, expecting the pain etc., in that way that it puts physiological functions in the best state of readiness to react on the threat or danger. Usual pain acts like an alarm for ANS to drive physiological functions in state well known as fight or flight. Contrary to this, in several research articles^{19, 28, 29, 37} it was shown that epifascial acupuncture (Japanese technique of fast needling in acupuncture points) produced therapeutic effects without pain and déqi effect. In addition, effectiveness of laser acupuncture, moxibustion, microwave resonant therapy and other techniques that are applied on acupuncture points without pain and déqi effect is challenging pain stimulus explanation.

Placebo effect

In several research paradigms there are results without significant difference between real and sham acupuncture^{20, 21, 16}. These results are recently used as the evidence that acupuncture does not create real therapeutic effects. Instead, placebo effect might be taking place not just in sham, but also in real acupuncture. Out of 38 articles on randomized controlled trials, published until 2009, Moffet⁴⁵ found that in 22 of them there was no difference between real and sham acupuncture (in 13 studies they were equally ineffective, in 9 they were equally effective). Zheng et al.⁴⁶ claim that without patient's expectation of therapeutic effect acupuncture is nothing more than ordinary mechanical hurting. It would mean that belief and expectation of patients transform needling into therapeutic procedure. Ker et al.⁴⁷ assume that expectation and attention focused on certain points on the skin might have specific effects on neurons in region of primarily somatosensory cortex that corresponds to location of these points, even before touch or stimulation of it really happen. Cognitive perception and processing stimulation often take place in ambient of ritual relationship of physician and patient, which represents certain amount of suggestion. State of the art is the fact that acupuncture research so far is not overcoming "the placebo barrier" (conclusion of majority of review papers that effect of acupuncture is not better than placebo)⁴⁸. Anyhow, in review article of Enk et al.⁴⁹ it was shown that there was a difference in analgesic effects of acupuncture in respect to sham acupuncture. Furthermore, some researches compared acupuncture with drug therapies, but their clinical settings were of poor quality, and in contrast with acupuncture practice⁴⁸. It turns out that trends in research are influencing on effect of sham acupuncture. In earlier research sham acupuncture was conducted with ordinary needling in non-acupuncture points. Then, minimal needling and dose of stimulations were applied. Finally, last few years the researchers use nonpenetrating needles (fake needling) in non-acupuncture points. It would be logical to expect that these changes of sham method should cause de-

creasing of its effect (placebo) during time. But, We et al.⁵⁰ gave evidence that there is an increase of sham acupuncture effect as its date of publication is closer to the present time. After reconsidering all possible factors they think that it is probably due to method of article selection for publishing in journals. Anyway, future researches have to solve the mechanisms of placebo effect; especially the relationship between expecting therapeutic effect of acupuncture (relief of symptoms), voice suggestion of doctor and autonomic placebo effect⁵¹. It means that experiments should be designed to contain comparison with sham acupuncture and clinical procedure without acupuncture. That is so, because some researches showed that both real and sham acupuncture could be more effective than classical therapy⁴⁵. These insights indicate that placebo effect is something more than subjective suggestive effect or spontaneous remission. Good results made by intentionally placebo therapies are supporting this assumption^{40, 52}. Ten years ago Sherman and Hickner⁵³ showed that many physicians in the United States from time to time prescribe or administer placebo to patients, *ie* as a supplemental treatment. Recent neurocardiological researches⁵² have shed a new light on placebo since it is not reasonable any more to consider placebo as just suggestion that afterwards creates psychosomatic effect. Placebo creates clinical result, not just as a result of expectation but also by means of information influence⁵⁴. A sort of this information influence is, primarily, not physiological, but physical. Information for therapeutic action could be coded on nano level of structural organization of biomolecules and water⁵⁴. Hence, some questions are plausible to be asked about, like: is any expectation or any suggestion going to work without such corresponding information? Or maybe expectation and suggestion can create (incode) such information? Bearing this in mind, even if without doubt modern researches discover significant role of placebo in acupuncture mechanisms, it does not mean that acupuncture is 'placebo' method and that AS (jīngluò) does not exist. On the contrary, along with this analogy other therapeutic methods could be discredited by means of placebo effect power.

Mechanistic model

Yang et al.⁵⁵ assumed mechanistic model of AS (jīngluò) based on forwarding mechanical disturbance from needling muscle tissue through mechanoreceptors and gap (Ca²⁺) junctions. Registered by them on MRI, sound wave (mechanistic process), artificially created with special needle on acupuncture point GB35 was propagating in longitudinal direction two times faster than in transversal. Afterwards, they investigated possibility of sound wave to activate cells of fibroblasts, that are known as mechano-sensor cells. Therefore, they recorded propagation of Ca²⁺ wave in cells fibroblasts. Certain distance ionic wave traveled for 230 s, which was much slower in respect to sound wave that activated the ionic wave. This result served them to conclude that action of acupuncture is not electrical or nerve-impulse but mechanistic in nature⁵⁵. Thus, in their opinion qì is a mechanical wave that animate all other physiological activi-

ties in organism (the model of process). They hypothesized the muscle model as a structure of AS (jīngluò). In further, qì is manifested in blood flow through mechanical pressure wave whose origin comes from the muscle of heart and blood vessels. Their explanations are congruent with principles of TCM⁵⁵.

Fascia

Considering recent publications, fascia is one of the most actual structures that is assumed as anatomical base of AS (jīngluò). It is a membrane-like structure³, enclosure and soft component of connective tissue that forms a continual matrix; it penetrates and surrounds all organs, muscles and nerve fibers⁵⁶; so, it is considered as a communication network since it influences, and is under the influence of all organs, blood vessels and nerves⁵⁷. Cytoskeleton of fascia is able to transfer mechanical forces. Applied on cytoskeleton mechanical forces produce biochemical cellular changes through mechanochemical conduction⁵⁶. Therefore, qì is a physiological movement and activity (in general); déqì could be understood as arrival of movement, sign that fascia reacted on acupuncture stimulation. Acupuncture fixes the blockage, sustains needed movement and renovates disturbed activity of fascia. Thus, movement is not just a propagation of signal, but also a travelling of mechanical wave through meridians⁵⁵. That is only part of the explanation, since there are evidences of propagation of light, electromagnetic and other waves through meridians^{1, 38}. It was shown, on software constructed models of human body, that areas rich with tissue of fascia are closely identical by location with TCM maps of meridians and points⁵⁷. Effective acupuncture places are identified with fascia that contains nerve endings, fibroblasts, undifferentiated mesenchymal cells and lymphocytes. Fascial anatomy is comprised of two systems: retaining one, made of undifferentiated cells of connective tissue with passive function of sustaining the nutritive ingredients and cells for functional system (yīn); and functional system, comprised of differentiated cells that have active function of maintenance of metabolic and life functions (yáng)⁵⁷. Thus, if fascia is biological base of AS (jīngluò) it is going to be crucial to explore correlation of activities in fascia with autonomic functions (nerve signals and electroconduction) especially because fascia is highly innervated with nerves of ANS⁵⁶.

Model of complementary analogy of autonomic nervous system and acupuncture system

Software visualization of sympathovagal balance by means of electrocardiography (ECG) monitor instrumentation has patterns very congruent with rules of yīn and yáng coordination in TCM^{1, 58, 59}. Sympatho-vagal balance of neurocardiology could be seen as complementary analogy with cang fu (zàngfǔ, 臟腑) concepts of TCM according to which all organs are connected through meridians of AS (jīngluò) and they relate with each other as yīn and yáng; qì has exact time of passing through each organ. Overactivity/deficit of

yīn or yáng are reflected in form of symptoms of diseases of organs/organism¹. It is in agreement with mechanisms of sympathetic and parasympathetic influence both on circulation function of cardiovascular system^{7, 12–14, 60, 61}, and regulation of other organs. Activity of one is usually followed with inhibition of other. It is governed by CNS and peripheral reflex mechanisms⁶¹; while sympathetic (s) ANS increases, parasympathetic (p) ANS decreases physiological functions (heart rate, blood pressure). Therefore, in general terms, sANS and pANS could be modeled as yáng and yīn, respectively. In that manner, concepts of TCM has complementary analogies with concepts in neurocardiology: organic dysfunction and syndromes (qiè, zhèng)⁶² are analogue with neurocardiological evaluation of states of ANS in various diseases; drop of qi (syndrome of qi deficit) is analogue with malfunction of autonomic regulation (very low value of total power of HRV spectra; it is used as predictor of sudden cardiac death); excess of yáng can be regarded as sympathetic predomination (high value of low frequency component of total power of HRV spectra); excess of yīn can be regarded as parasympathetic predomination (high value of high frequency component of total power of HRV spectra)^{58, 62, 63}. From these analogies, it turns out that qi could be functionally characterized by means of spectral parameters of HRV, where cardiovascular ANS has a role of functional mediation between AS (jīngluò) and CVS and, potentially, with other organ systems^{38, 58}.

Neurocardiovascular system and qi regulation

After review of researches in this paper, it should be evident that effects of acupuncture include action of ANS, CNS, endocrine system and other mechanisms. But, there are

no clear suggestions about histological structures of AS (jīngluò). Based on these results it is not reasonable to identify AS (jīngluò) with ANS. Development of ANS starts in the third week of embryogenesis⁶⁴, while regulation processes are present earlier, even before formation of any organ system. Some research assume AS (jīngluò) as the first regulating and developing system of a number of synchronous, simultaneous, coordinated and precise embryonic processes^{64–67}. After all, evidences of physical existence of AS (jīngluò) do exist: diseases of acupuncture system are sometimes expressed in the form of skin changes that are following lines of diseased meridians³. In the moment of deqi sensation, acupuncturists claim that occasional meridian might react by delineating through the skin. Also, there are experiments in which propagation of sensations across meridians was detected, as well as movement of isotopes³. However, detection of qi flow by means of any scientific method has not been done so far. Despite of it, qi flow is possible to experience and sense just like gravitation force is, no matter that gravitation is also not detectable by scientific methods. By TCM practice qi flow could be awarded. It serves even for intentioned regulation of heart rate and blood pressure (meditative breathing and exercise, qigōng). Vitality of qi is basically under the influence of stress and emotions^{1, 38, 68–70}. Relation of emotions and CNS modern research has confirmed without doubt. It is well known that brain contain network of neuronal system responsible for processing of emotion. It is called limbic system and it is directly correlated with regulating neural networks for heart regulation⁶⁷. Based on this, we can derive and illustrate one hypothetic model of qi regulation that is in the base of acupuncture mechanisms (Figure 1).

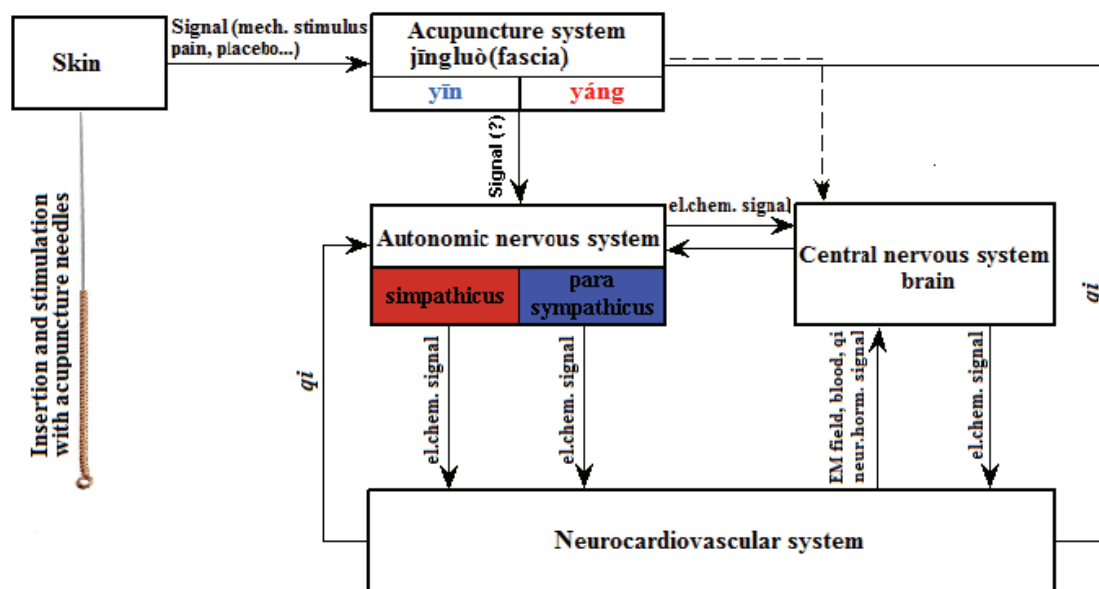


Fig. 1 – Summarizing hypothetical model of qi regulation by acupuncture: acupuncture needling and stimulations (pulling in and out, rotations of needles) creates some sort of signal (mechanical microstimuli, pain, placebo, etc.) that affects acupuncture system (fascia). From fascia, signal is forwarded through its innervated structure to autonomic nervous system (ANS). ANS sends signal to the brain that processes these informational inputs and feeds back the information to ANS in order to prepare cardiovascular system for responding to the environmental stimuli, in other words, to regulate physiological functions (e. i. blood pressure and heart rate).

Conclusion

The scope of this article was to evaluate the results of different studies on biophysical basis of AS (jīngluò). To our knowledge it represents the first theoretical survey in which hypotheses of acupuncture mechanisms were summarized from an overview of research results in articles about influence of acupuncture on ANS. However, it could not be a systematic overview nor a meta-analysis, due to the high heterogeneity of researches on related topic. Also, there was intention to analyze the topics from various points of view with different kinds of results. Mechanisms of acupuncture are not scientifically explained even in China from where acupuncture originated. More comprehensive experimental research is needed in order to evaluate all the theories of AS (jīngluò). By means of correlations of therapeutic effects of acupuncture and parameters of heart rate variability (that reflects autonomic functions) it is possible only to assume existence of functional dependence of AS and ANS. In general, our remarks are congruent with fascia as most probable candidate for acupuncture system in physical sense. Structures of fascia might receive needle inserting in form of stimuli which is by nature something among neural stimulus, pain, microme-

chanical movement or placebo, as overviewed in previous sections. Then, it is logically to suppose that fascia transforms these stimuli into some kind of signal ($\approx qi$) and afterwards transfers it to ANS that lead to better regulation of physiological functions. From final perspective related with relief of disease symptoms we consider it in terms of therapeutic effects of acupuncture. In that manner, state of ANS could be significant factor of effectiveness of acupuncture therapy. Thus, besides scientific significance, this research reinforces the progress of integrative biomedical approach of two complementary medical systems - western world medicine and traditional Chinese medicine, aiming more successful diagnostics and therapy of various diseases.

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