



Psychoneurobiomodulation: an emerging concept to understand the systemic effects of neurophysiological acupuncture

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Abstract: Acupuncture is a therapeutic approach that emerged from traditional Chinese medicine. The World Health Organization recommends the use of acupuncture for the treatment of a wide variety of diseases. Experimental evidence suggests that the working mechanism of acupuncture may include the activation of multiple regulatory systems in the organism including the nervous system. In the present article we propose the concept of psychoneurobiomodulation to describe the local and systemic effects of acupuncture treatment. The concept emerges from current evidence for changes produced by acupuncture in the area of needle insertion (biomodulation), in distinct areas of the central nervous system (neuromodulation), as well as the modification of neural networks related to psychological responses, such as affective states, behavior, and higher brain functions (psychoneuromodulation). This concept could also be applied to include interventions of systemic modulation that have as an objective the restoration of balance in the organism in situations of stress or illness.

Keywords: Acupuncture; modulation; neuromodulation; neurophysiology; psychoneuromodulation

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Introduction

Life results from a multifactorial dynamic equilibrium in the biological, physical, and chemical processes that occur on our planet (1). From the perspective of traditional Chinese medicine (TCM), the universe results from the balanced expression between two antagonistic but complementary qualities, designed as Yin-Yang (2). In this sense, day (yang) occurs transiently to allow night (yin); which allows the succession of day and night. Such events modulate our daily activities and synchronize our rest and activity cycles, including hormonal and physiological rhythms as

well as cognitive processes (3). To maintain this temporary organization and the dynamic equilibrium of nature, self-regulating, adjustment and/or modulating mechanisms are required, which interact with each other and act with different degrees of complexity (1).

Cells and systems of the human organism also present intrinsic and complex mechanisms of modulation and their physiological activity remains within ranges of constancy (4). Recent evidence indicates that alterations in the mechanisms of modulation constitute the common denominator of various chronic degenerative pathologies (5-9).

Acupuncture is a curative and preventive treatment

of TCM, which involves the introduction of fine needles in specific sites of the body, called acupuncture points (10). From the experimental perspective, it has been demonstrated that acupuncture increases the capacity of self-regulation and/or modulation at multiple scales to maintain or restore homeostasis and therefore prevent or treat diseases (11,12).

This article proposes the concept of psychoneurobiomodulation in order to integrate local and systemic mechanisms, triggered by acupuncture and its stimulation variants. This conception is constructed from the current evidence of cellular changes evoked by acupuncture at the puncture site (biomodulation), as well as by activation of multiple systems, including the central and autonomic nervous system (neuromodulation) and changes in the activity of neural networks related to psychological responses and superior brain functions (psychoneuromodulation).

Biomodulation

It is known that biomodulation is related to the associative or reactive adjustment of the cellular or biochemical status of an organism, with as an objective to maintain constant its internal environment or to increase the adaptability to stressors (13). Modulating events typically consist of the interaction of body tissue with molecules (biomodulators) that modify the response of an effector (14). For example, endorphins modulate the inflammatory response, producing changes in the activity of immune cells (15). Accordingly, biomodulation induces changes in gene expression, protein synthesis, enzymatic activity, production and release of hormones, growth factors, cytokines, cell differentiation and proliferation, processes of relevance in the preservation and maintenance of tissues (16-18).

To induce biomodulation, antagonistic but complementary (in terms of TCM denominated Yin-Yang) effectors are required, that is, modulating mechanisms of biological processes that may be expressed at various levels, from the microscopic (atomic, molecular, cellular) to the macroscopic (systems in the body) appear to be coded in a binary way. For example, the inflammatory response is modulated by pro-inflammatory and anti-inflammatory cytokines, which constitute an important route of communication that allows the cellular response to inflammation to be amplified or diminished (18).

The inflammatory response is homeostatic when pro-inflammatory cytokines (yang) such as tumor necrosis factor

(TNF) and interleukin (IL)-2 are produced in adequate amounts. Otherwise, the excess can lead to chronic inflammation, chronic stress with failures in the recovery mechanisms, hypersensitivity pathologies, autoimmunity and constitute a risk factor for various chronic degenerative pathologies (18). The inflammatory response is also biomodulated by regulatory T cells, M1, M2 macrophages, and anti-inflammatory cytokines (yin), such as IL-4, -10, -13, -24 (18,19). Its activity is important for immunological tolerance and is currently a therapeutic target for different pathologies (20).

The body also includes epithelial cells, residents of connective tissue, neurons and muscle cells, whose activity is regulated by growth factors, cell death inducers, excitatory neurotransmitters, inhibitors, neuropeptides, among others.

Experimental evidence has shown that acupuncture produces significant changes in the puncture site to restore balance in the organism through biomodulation (11,14,21). In particular, when the acupuncture needle is introduced, cellular responses at the puncture site constitute biomodulatory mechanisms that are being activated.

Locally, epithelial cells, immunological cells, muscle cells and other residents of the connective tissue assume a relevant role. Traumatized epithelial cells release bradykinin, substance P and prostaglandins, which activate and recruit mast cells, macrophages, neutrophils and eosinophils at the site of damage (21). The immune cells release substance P and histamine, to increase vascular permeability and favor the recruitment of cellular elements such as neutrophils. It has been shown that after introducing the needle into the skin, blood flow and local temperature are increased (22).

These changes are seen clinically as erythema in the areas adjacent to the puncture (15). The immune, epithelial and fibroblast cells release growth factors that participate in the remodeling of damaged tissues. The epidermal growth factor (EGF) and angiogenic growth factor (AGF), induce wound healing and the regeneration of muscle fibers. These factors also participate in the regenerative processes of acupuncture for the treatment of skin lesions and striated muscle (23). Likewise, the pro-inflammatory response is modulated and it has been demonstrated that the pro-inflammatory response triggered by the puncture is inhibited by the release of anti-inflammatory cytokines such as IL-10 and the production of T-regulatory lymphocytes (18). Here we can see a balance in the yang excitatory mechanisms (inflammation) and yin inhibitors (anti-inflammation), that is, biomodulation at the puncture site.

The cellular response to acupuncture also depends

on the coupling of the needle to the extracellular matrix. The cytoskeleton of the fibroblasts is attached to the collagen fibers of the extracellular matrix by integrin and laminin proteins (24). Such coupling allows the fibroblasts to produce responses such as cell contraction, migration and synthesis of growth factors in response to mechanical pressure or deformation of the extracellular matrix. When the needle is introduced in the subcutaneous tissue and then rotated, the tissue adheres to the needle, following the rotation until it forms a spiral of connective tissue (25). Consequently, fibroblasts and collagen fibers align around the longitudinal axis of the needle, actin filaments polymerize, stress fibers are formed and growth factors are released (25). These changes are the basis of the phenomenon of grasp that is generated between the needle and the connective tissue, once the former is introduced and rotated at the acupuncture point; they are also the starting point for the mechanotransduction process, which serves to recruit cellular elements at the puncture site, to activate sensory receptors and afferent fibers and to send nerve signals from the periphery to the central nervous system activating the processing centers and triggering the systemic effects of acupuncture (11).

Neuromodulation

The patterns of neuronal activity are not static but variable and depend on the environmental conditions and the stimuli they receive (26). One of the processes that influence the activity of neural circuits is neuromodulation, which consists of activating (facilitating) or deactivating (reducing) synaptic contacts and their efficiency through changes in the expression of pre- and post-synaptic receptors, the release of neurotransmitter, the sensitivity of post-synaptic neurons, the level of neuron excitability as well as the properties of ion channels (27).

It has been demonstrated that the effect of acupuncture includes the activation of circuits formed by sensory receptors, afferent pathways, processing centers, efferent, and effector pathways (11). The processing centers integrate the responses to different levels of the central nervous system, such as the spinal cord, the brainstem, the diencephalon and the telencephalon (28,29). The degree of activation of such nerve centers determines the magnitude and effectiveness of acupuncture on organic functions. These effects occur due to the modulation by the autonomic nervous system, the neuroimmune and the endocrinological system (11).

In models of neuropathic pain, it has been shown that

electroacupuncture (EA), which is a variant of acupuncture, in which pulses of electrical current are applied through the needles, modulates multiple and interconnected systems of the organism. At the level of the spinal cord, EA activates serotonergic, adrenergic, cholinergic and opioid pathways; as well as presynaptic mechanisms associated with the depolarization of primary afferents (15,29). It has also been shown that their effects extend to the neuroglia (28). At the gastrointestinal level, acupuncture has been shown to modulate peristalsis, visceral sensitivity, the gastrointestinal barrier, and the gut-brain axis (30) and also the participation of neuromodulation centers located in the spinal cord, brain stem and the dorsal motor nucleus of the vagus has been demonstrated (31). The dual regulatory effects of acupuncture are manifested by promoting gastric peristalsis in subjects with low initial gastric motility and suppressing peristalsis in subjects with active initial motility (32). The regulation of acupuncture in gastric motility is dependent on the intensity and frequency of the stimulation (32).

Acupuncture also neuromodulates the integrative centers of cardiovascular responses (33,34) and blood flow (35,36), and has functional implications in the treatment of diseases such as hypertension (37), anxiety, vascular dementia (38) circadian rhythm disorders, polycystic ovarian syndrome and infertility (39,40).

In the case of dysautonomia, a cluster of various diseases caused by the imbalance between sympathetic and parasympathetic activity, evidence is also emerging that acupuncture modulates the expression of receptors and the release of neurotransmitters in order to generate an adaptive brain state that improves the autonomic response (41).

Psychoneuromodulation

The study of the mechanisms that underlie spontaneous thinking, associated with specific tasks, the dynamics of the mind, attention, intelligence, motivation, emotion, conscience, personality and behavior, constitute relevant topics in the field of psychology and neuroscience (42). The neuronal doctrine establishes that the neuron is the structural and functional unit of the nervous system (43,44). This doctrine provides a conceptual basis for neuroscience and allows to understand the ionic bases of neurotransmission and synaptic integration. However, new methods that allow to record multineuron activity have revealed that sets of neurons or neural networks, instead of individual cells, form the physiological units and generate

the emergent functional states that can be associated with behavior and emotions (43). It is also these collective properties that participate in higher brain functions such as memory, cognition, and language.

Neural models include the neural default network, the neocortical-paralimbic-limbic network, the sensorimotor network, the dorsal attention network, the executive control network, the visual neuronal network, the auditory neuronal network and the outgoing neuronal network (42,45).

Psychoneuromodulation corresponds to the modification of the activity of neural networks related to psychological responses, such as affective states, behavior, coping mechanisms, as well as superior brain functions. It allows the development of skills and competencies for conscious emotional control and achievement of goals (42).

Recent studies have shown that acupuncture modulates the activity of different neural networks, such as the neural default network (20,46,47), the neuronal motor-cortical network (48), as well as different regions related to cognition (49), the neocortical-paralimbic-limbic network (50), and the frontoparietal left network (32). Such changes are accompanied by modifications in the cognitive, emotional and behavioral responses including higher brain functions.

Other studies have shown that acupuncture activates large regions of the brain related to emotional regulation, such as the dorsolateral prefrontal cortex, the cingulate cortex, and the periaqueductal gray matter (51). There is also clear evidence that acupuncture can reduce neurological and psychological symptoms, in pathologies such as Parkinson's disease, Alzheimer's, cognitive impairment, depression, migraine, schizophrenia, autism, pain and depression (52-54).

Psychoneurobiomodulation

Evidence abounds on the effects of acupuncture at the local and systemic levels. Such effects occur at multiple levels of complexity, whose common denominator are the endogenous modulatory mechanisms of cellular, neuronal, neural networks and behavior.

As described above, acupuncture biomodulates distinct cellular responses at the puncture site, immunomodulation, modulation of connective tissue and extracellular matrix, including the release of vasoactive mediators. However, the effects of acupuncture are not restricted to the puncture site but they are transmitted by different humoral and neurophysiological mechanisms to the processing centers

of the central nervous system, to activate the mechanisms of systemic neuromodulation, including those neuronal circuits related to affective states and higher brain functions.

A concept that encompasses the local and systemic modulating effects of acupuncture is psychoneurobiomodulation, which corresponds to the reactive adjustment of cellular, neuronal and systemic status, which includes neural networks related to psychological responses, to maintain or restore homeostasis and therefore prevent or treat disease. Such changes occur due to the release of modulating substances induced by acupuncture, with antagonistic but complementary actions (32,46,47,55).

This concept could also be applied to all those interventions of systemic modulation (meditation, massage, psychotherapy, aromatherapy) that induce electrochemical, neurobiological and psychological changes, which in turn increase the self-regulation of the body leading to wellbeing and health including mental, social and spiritual aspects.

It has now been shown that the interrelation of systems in the organism not only determines the biological aspect but is also closely related to the functioning of the mind, affective states, motivation, higher cognitive functions, including intuitive decision making. Summarizing, psychoneurobiomodulation encompasses a concept that allows the acupuncturist to understand that acupuncture treatment goes beyond a simple modulation of the cellular, visceral and/or organic response but also impacts the affective, emotional and cognitive spheres of the patient, so that through its endogenous mechanisms it may result in the prevention and the recovery of disease.

Conclusions

Psychoneurobiomodulation is an emerging concept that integrates the systemic effects unleashed by acupuncture. This term is constructed from the current evidence about the changes produced in the puncture site, in different areas of the nervous system, as well as the modification of the activity of neural networks related to psychological responses, such as affective states, behavior, coping mechanisms and superior brain functions.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/lcm.2019.12.01>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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