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Review Article

Recent Approaches on Signal Transduction and Transmission in Acupuncture: A Biophysical Overview for Medical Sciences

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Abstract
Acupuncture is one of the areas among the alternative therapies that arise high curiosity in the biomedical scientific community. It is particularly popular for treatment of chronic diseases and addictions. However, contrasting with its evidence-based effectiveness, the lack of reasonable explanations for its mode of action divides that scientific community. Difficulties also arise to those responsible for providing information for clinicians and professionals who wish to acquire competencies leading to the acupuncture practice and have a background based on biochemistry and physiology. The classic theories of nerve conduction do not fully explain how information is read and transmitted during the acupuncture treatment. Other theories have been proposed, but they are based on concepts such as biophotonic waves and quantum biochemistry that are difficult to read and understand by those who do not have knowledge in physics. It is the main objective of this review to provide a summary of the main theories and explanatory approaches to the signal transduction and conduction in acupuncture and to describe them in terms of their explanatory hypotheses, limitations, and weaknesses.

The most of the literature found support theories for neural conduction, including gate control. They explain the effects of acupuncture in pain relief; few studies have been conducted concerning the conduction based on biophotons. The primo vascular system has been referred as a possible anatomic support for conduction of information during an acupuncture treatment, which could be connected to biophoton transmission.

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Abbreviations

5-HT	5-hydroxytriptamine
APtN	anterior pretectal nucleus
Arc	arcuate nucleus
BHC	Bonghan corpuscles
BHD	Bonghan ducts
BHN	Bonghan nodes
BHS	Bonghan System
CNS	central nervous system
cPN	communications primo nodes
ePVS	external primo vascular system
Hab	habenular nuclei
HAR-NDS or NDS	Hyaluronic Acid-rich Node and Duct System
iPVS	internal primo vascular system
LC	locus coeruleus
NRM	nucleus raphe magnus
oPN	organic primo nodes
PAG	periaqueductal gray matter
Po	preoptic area
PVS	primo vascular system
PVs	primo vascular vessels
rPN	receiving primo nodes
RVM	rostral ventromedial medulla
Sm	nucleus submedius
VLO	ventrolateral orbital cortex

1. Introduction

Acupuncture is one of the areas among the alternative therapies that have been most investigated by the biomedical scientific community to study and test its effectiveness [1], at least in particular conditions such as chronic diseases and addictions [2]. Even so, the lack of reasonable explanations for its mode of action somehow contrasts with the evidence-based effectiveness, which divides the medical and scientific community, especially in countries where acupuncture is not a recognized practice but yet is used as a complementary therapy by the National Health Services. Difficulties also arise in the community responsible for providing information for clinicians and professionals who wish to acquire competencies leading to the acupuncture practice and have simultaneously a background based on previous knowledge of biochemical and physiological processes as well as anatomical structures of the human body. A serious question arise: if it works, how does it work?

Despite recent research using sophisticated equipment, most of the mechanisms triggered by acupuncture have not yet been clearly elucidated. It has been known for a long time that acupuncture points have distinct anatomical and electrical characteristics from the remaining surrounding tissues [3-5] but acupuncture practice is still mostly based on evidences. For most of the Western biomedical community, when a system is stimulated and a consequent response is achieved, somewhere a path must exist for signal recognition and signal transmission to and from a decision-making structure. Studies utilizing positron emission tomography scan technology have verified the linkage of distal acupuncture points to correlating brain centers and demonstrated the homeostatic effects of acupuncture [6] showing that the puncture by a foreign object induces related brain activity. However, the various theories trying to explain the pathway taken for the action are far from providing an ultimate answer to the question. It is the main objective of this review to provide a summary of the main theories and explanatory approaches to the signal transduction and conduction in acupuncture. These will be described and analyzed in terms of their explanatory hypotheses, as well as their limitations and weaknesses.

2. The ancient theory

In accordance with the original oriental concepts, the energy *chi* obtained by a purgative process similar to digestion is spread to the body "organs" through a network of "vessels, channels, or meridians"-the *jing mai*, which are located deep beneath the skin and carry the internal energy, the *zhang qi*. Those vessels would be connected to another network of "vessels" running superficially at skin level, called body meridians vessels-the *luo mai*. The latter ones have the property of being externally accessed in locations named acupoints, as explained succinctly by Kovich [7]. In accordance with the ancient thinking, the external energy *xie qi* can be captured by exterior receptors that are a part of the superficial network channels *luo mai* and can be converted into electric, magnetic, or biochemical energy. The development of an illness starts when there is a prevalence of the *xie qi* over the *zang qi*. The body has an auto-repair capacity and in order to that repair to occur the correct stimuli should be transmitted by the interior / exterior system (*biao-li*). A correct balance between the *xie qi* and the *zang qi* may be archived by stimulation of the acupoints.

3. The acupoints and mechanisms of signal transduction

In accordance with the old fundamentals of acupuncture, the acupoints are singular areas in the skin that have been identified as being the external accessible places related with internal organs. As such, they are envisaged as sites for cutaneous manifestations of the loss or alteration of the functionality associated to the corresponding organ and have the property of modulation of their neurophysiology, under proper stimulation.

Kim *et al* [8]. suggest that acupoints are indeed cutaneous neurogenic inflammatory sites. They assumed that acupoints are associated with the noxious sensory signals from visceral organs. They detected and mapped, using Evans blue dye, places on the skin connected to the small intestine in an animal model with colitis. Kim et al [8]. showed that some, but not all, acupoints are neurogenic spots. According to them, stimulation of neurogenic points prevents the development of the disease associated with that point at a higher frequency than if the same stimulation is made at the nonneurogenic acupoint or at the control.

The electrical potential of the human epidermis ranges from 20 to 90 mV. When high-density sensorial nervous terminations are present, the epidermal potential is higher. The main biophysical property attributed to acupoints is the higher electric conductance than in the neighboring areas [9,10]. Recent studies pointed out the relation between the high conductance at acupoints and the release of the neuropeptides substance P (SP) and calcitonin gene-related peptide (CGRP) during neurogenic inflammation in a painful area [11].

Acupuncture lowers the resistance of the area and increases the electric flow. Most of the acupoints are located adjacently to or on peripheral nerve trunks or branches, nerve receptors or endings, capillary, blood or lymphatic vessels and mast cells [12].

Peripheral stimulation in the acupoint may induce muscle contraction or injury and/or mechanical movements into connective tissue. It has been earlier suggested that the acupuncture feeling of *"De qi"* owes its origin to induced impulses coming from muscle tissue or other deep tissues that have polymodal-type receptors. When muscle tissue is injured locally, this leads to the release of proinflammatory mediators that excite the nociceptors, stimulating the conduction via C-type afferents. Other authors consider that mechanical action on connective tissues, in particular the winding of the tissue around the needle during rotation, would induce the degranulation of mast cells involved in analgesia [12-15].

4. Theories on signal transmission

4.1. The neural conduction

Some meridian paths are roughly related with nerves, e.g., the lung meridian with the median nerve; the pericardium meridian with radial and medial nerves; the bladder and stomach meridian with the perineal nerve. Those nerves would act as a physical support for neural conduction [16].

The primary stimulation for neural conduction is the nerve receptors or endings or the peripheral nerve trunks or branches. Indeed, it seems that there are particular central nervous pathways gathered by acupuncture that are based on experimental evidence: after its introduction in the acupoint, the needle could reach the neural receptive field and trigger skin and muscle sensory receptors that are able to transmit sensory perceptions to first- and second-order neurons located at spinal and supraspinal levels [17]. The hypothesis is based on the fact that when lesion of nerves occurs (locally, at the spinal cord, or at the supraspinal regions) or when neuronal activity is blocked, the action of acupuncture is reduced or disappears. This has been observed on functions of the following systems: cardiovascular [16], nociceptive or nonnociceptive pathways [18], immune responses [19,20], digestive system [21], and neuroendocrine regulation [22].

4.1.1. Gate control for endogenous pain modulation

The gate control theory systematizes the mechanisms inherent to the control and transmission of the sensation of pain based on the nervous conduction. This pathway for signal transduction and transmission is well documented and also explains some of the mechanisms of pain relief gathered by acupuncture. In short, it shows that mechanical or electrical stimulation by needling at the acupoint leads to the liberation of endogenous substances that are, in turn, responsible for inhibition of pain sensations [2].

The neural mechanisms related with acupuncture analgesia were revised in 2008 by Zhao [23]. Most of the information coming from the nociceptive afferent fibers is transduced in excitatory discharges of multireceptive neurons in the central nervous system (CNS). It has been shown that when acupuncture is used to relieve the pain, the CNS gets impulses from the afferent fibers located at the pain region and also from those located at acupoints. There are several types of afferent nerve fibers activated by acupuncture. Manual acupuncture activates the fast-conducting myelinated Aβ and Aδ and the slow-conducting unmyelinated C, particularly when muscle tissue is injured locally by needling, because this action permits the release of proinflammatory mediators such as histamine and 5-hydroxytriptamine (5-HT), and electroacupuncture, depending on the frequency, activates Aβ and some of the Aδ afferent fibers [24]. Those signals ascend to the cerebrum or hypothalamus, enabling the pain modulation. In addition, some acupoints show specific functional activities related with mechanisms occurring in the spinal cord. Spinal pathways of impulses coming from acupoint needling ascend mainly through the spino ventrolateral funiculus.

At the CNS, a set of nuclei structures involved in the process of pain control are stimulated by acupuncture [25] (Fig. 1a): (i) the rostral ventromedial medulla (RVM) [mainly the nucleus raphe magnus (NRM)] and the periaqueductal gray matter (PAG) that are known by their role in gate control, (ii) the nucleus submedius (Sm), and the (iii) the locus coeruleus (LC). The last two have been lately referred as alternative paths of the descending inhibitory system for control of pain frequencies and intensities. Several neuromodulators such as endogenous opioids (endorphin, encephalin, endomorphin, and dynorphin) and serotonin (5-HT) are involved and act as inhibitory mediators. High-frequency electroacupuncture stimulates the liberation of dynorphin, the natural ligand for the κ-opioid receptors, and low-frequency electroacupuncture stimulates the release of β-endorphin, encephalin, and endomorphin that can activate the μ- and δ- opioid receptors [26].

At the spinal cord, powerful inhibition of pain-related information may occur. These inhibitory systems can be activated by brain stimulation and peripheral nerve stimulation.

The RVM and PAG are structures rich in opioid receptors and form an axis that is critical in the mediation of endogenous analgesia because they control the descending mechanisms for pain modulation (Fig. 1a). The PAG receives inputs from the prefrontal cortex, hypothalamus, and amygdala and projects them to the RVM. It is also able to send efferent connections to the NRM when stimulated by opiates (endogenous or otherwise). Opiate analgesia is mainly mediated by neurons in the RVM. Both the NRM and RVM project profusely via the dorsolateral funiculus to superficial and deep laminae in the dorsal horn, giving direct inputs to the spinal dorsal horn and several supraspinal sites.

When stimulated, the raphespinal neurons release serotonin and project to enkephalin-releasing opioid interneurons (either enkephalin or dynorphin) in the posterior horn of the spinal cord that, by their turn, are able to make inhibition of pain in the spinal cord as follows (Fig. 1b): they activate the opioid receptors on the axons of incoming C and Aδ fibers that transmit the pain signals from nociceptors activated in the periphery. The activation of the opioid receptor leads to the inhibition of the release of substance P and thus inhibits the activation of the neuron that is responsible for transmitting the pain signal up the spinothalamic tract to the ventroposterolateral nucleus of the thalamus. This is the basis of the gate control theory, in which the pain sensation disappears since the nociceptive signal is inhibited before it is able to reach the cortical areas that interpret the signal as "pain" [27].

Recently, some studies [28] have also provided evidence for the involvement of the medial thalamus nucleus submedius (Sm) in modulation of nociception. This evidence indicates that the Sm, the ventrolateral orbital cortex (VLO), and the PAG also constitute a pain modulatory pathway (the Sm-VLO-PAG pathway), which plays an important role in the analgesia induced by electroacupuncture stimulation of the acupuncture point for exciting small-diameter fiber (Aδ and C group) afferents. Opioid peptides, serotonin, dopamine, glutamate, and their related receptors are involved in Sm- and/or VLO-mediated descending antinociception, and a GABAergic disinhibitory mechanism participates in mediating the antinociception induced by activation of the μ opioid receptors, serotonin 1(A) receptors, and dopamine D(2)-like receptors [29,30].

The third site in endogenous pain modulation and stress that is related with acupuncture is the noradrenergic LC nucleus. The LC is responsible for mediating symptoms associated with stress arising from sympathetic effects once it responds to an increasing norepinephrine secretion that will alter cognitive function (through the prefrontal cortex), increase motivation (through nucleus accumbens), activate the hypothalamic-pituitary-adrenal axis, and increase the sympathetic discharge/inhibit parasympathetic tone (through the brainstem).

4.1.2. Additional features beyond analgesia

Apart from the areas of the CNS already mentioned, it has been suggested that acupuncture interferes with further structures related to brain activities other than pain. Those comprise the arcuate nucleus (Arc), the preoptic area (Po), the anterior pretectal nucleus (APtN), the habenular nuclei (Hab), and the amygdala.

The Arc of the hypothalamus includes diverse populations of neurons that help mediate different neuroendocrine and physiological functions. It is responsible for

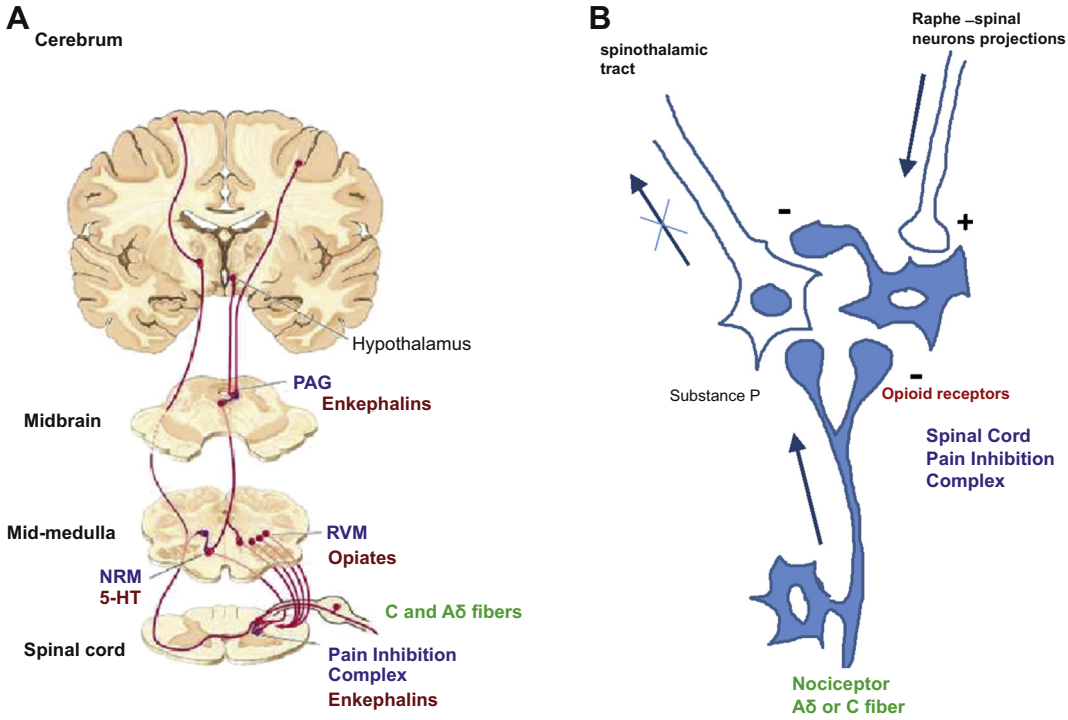

Figure 1 Basis of the gate control theory. (A) General view. (B) Pain inhibition complex in detail. In short, the stimulation of the PAG in the midbrain activates neurons that are able to release enkephalins and project to the brainstem, specifically in the raphe nuclei (NRM) where 5-HT (serotonin) is released and descends to the dorsal horn of the spinal cord. The 5-HT is able to activate interneurons that, by their turn, release endogenous opioid neurotransmitters (either enkephalin or dynorphin in (B)), which activate the opioid receptors on the axons of incoming C and A-δ fibers that transmit the pain signals from nociceptors activated in the periphery. 5-HT = 5-hydroxytriptamine; NRM = nucleus raphe magnus; PAG = periaqueductal gray matter.

hypothalamic functions, such as regulating hormones released from the pituitary gland or secreting their own hormones so it is involved in homeostasis, as so, it provides the for the central integration in regulation paths of feeding, metabolism, fertility, and cardiovascular regulation.

The Po is responsible for thermoregulation and receives nervous stimulation from thermoreceptors in the skin, mucous membranes, and hypothalamus itself. This area propagates stimuli to either the heat-losing or the heat-promoting centers of the hypothalamus.

As part of the subcortical visual system, neurons within the anterior pretectal nucleus respond to varying intensities of illuminance and are primarily involved in mediating nonconscious behavioral responses to acute changes in light. In general, these responses involve the initiation of optokinetic reflexes, although the pretectum can also regulate nociception and rapid eye movement (REM) sleep [31].

Recent exploration of the habenular nuclei has begun to associate the structure with an organism's current mood, feeling of motivation, and reward recognition. The LHb is important in understanding the reward and motivation relationship, and it relates to addictive behaviors. The lateral habenula (LHb) inhibits dopaminergic neurons, decreasing the release of dopamine. Elevated dopamine levels seem to be associated with addictive drugs [32].

The amygdala plays a primary role in neurophysiological behaviors such as social interaction, experience of fear, anxiety, aggression, and posttraumatic stress disorders. They are also responsible for the processing of memory modulation, emotional learning, and decision-making processing and are considered part of the limbic system [33].

4.2. The primo vascular system (hyaluronic acid—rich node and duct system)

Originally identified by Bong-Han Kim [34] as the system correspondent to the acupuncture points and meridians, the primo vascular system (PVS), at the time named as the Bonghan System (BHS), comprised two main structures: the Bonghan ducts (BHDs) and the Bonghan corpuscles (BHC). Those structures were reinvestigated approximately 50 years later [35] by other researches including Soh [36], Stefanov and Kim [37], and Stefanov et al [38]. that were able to detected, with new techniques for coloration, corpuscles and ducts in adipose tissue and fascia [39] inside the blood vessels (caudal blood vena of rabbits and rats, abdominal arteries and veins, hepatic vein [40,41], lymphatic vessels of rats [42], human umbilical cord and placenta [43]), in the surface of internal organs [44,45], in the cerebrospinal fluid of brain ventricles [46], and in the spinal cord of rabbits [47] that were identified as being the BHD and Bonghan corpuscle described years ago by Kim Bong-Han. As a result of these new studies, the BHDs were renamed primo vascular vessels (PVs) and the Bonghan nodes (BHN), primo nodes (PNs) [37]. Stefanov and Kim [38] proposed on the basis of the confirmation of Bong-Han Kim's findings, to divide the PVS into external primo vascular system (ePVS) and internal primo vascular system (iPVS), see scheme in Fig. 2, based on the location of the vessels and nodes. Structures located superficially in the body as those found in connective and fat tissues (hypodermal layer, superficial fascia, epineurium and perineurium, vessel's adventitia, and fat tissue) are considered being part of the ePVS. Structures appearing in the organ-covering membranes (parietal and visceral peritoneum, pia mater, and arachnoidea) as well as those appearing in the internal cavities and lumens (brain cavities, heart chambers, blood and lymphatic vessels lumens, cerebral aqueduct, and spinal cord channels) are considered being part of the iPVS. Nodes located in the iPVS were envisaged as receiving primo nodes (rPNs), while nodes located in internal cavities and organs, as organic primo nodes (oPN). The rPN and the organic primo node are connected through the communicating primo nodes (cPN) (Fig. 2).

4.2.1. The primo vascular vessels

The histological features of the primo vascular vessels and nodes have been studied in the lymphatic vessels and in organ surfaces of mammals. So far, results point out that the PVs are constituted by a membrane with high concentration of hyaluronic acid and consist of several subchannels that have an endothelium membrane with rod-shaped nucleus cell and an adventitia that has connective tissue made of collagen [48] (Fig. 3a).

The stereomicroscopic images of the PVs, obtained in the cerebrospinal fluid of the brain ventricles, point for ducts of 20-40 μm in diameter carrying fluid with one-way flow with an average speed of 0.3 ± 0.1 mms^{-1}, measured by the velocity of spread of fluorescent nanoparticles [36,49]. It is believed that the movement of the fluid is maintained by the action of contractive cells in the walls of the vessels that seem to have resting potentials similar to the smooth muscle and are depending on Ca^{2+} channel depolarization. The cells of the PVS show smooth-muscle Ca^{2+}-excitable cells that are related to the movement. The vessels carry a liquid, the primo liquid with cells (monocytes, eosinophils, mast cells and macrophages [50], microcells [51,52], and stem cells, as well as several substances such as hormones and proteins [53]). The PVS has also several cells in mitosis stage and some other types of cells with DNA-containing granules that are typical of the PVS [54]. Stem cells have been found on the surface of PVs and PNs [55].

More recently, Kwon *et al* [44]. demonstrated that the PVs and nodes could be visualized with Alcian blue staining, which is typical of structures rich in hyaluronic acid. They renamed the PVS as hyaluronic acid-rich node and duct system (HARNDS or NDS). The ducts and nodes contain innate immune cells and hematologic progenitors and thus seem to be part of the immune system. It seems that the NDS selectively attracts the inflammatory macrophages and neutrophils, has a flexible structure just like the lymph node, and is structured with the fibroblastic reticular cells and reticular network. However, the immunological roles and physiological significance of the NDS are still not defined [57,58].

4.2.2. Acupuncture and PVS

Some authors consider that the NDS (PVS) is a third circulatory system corresponding to the ancient acupuncture

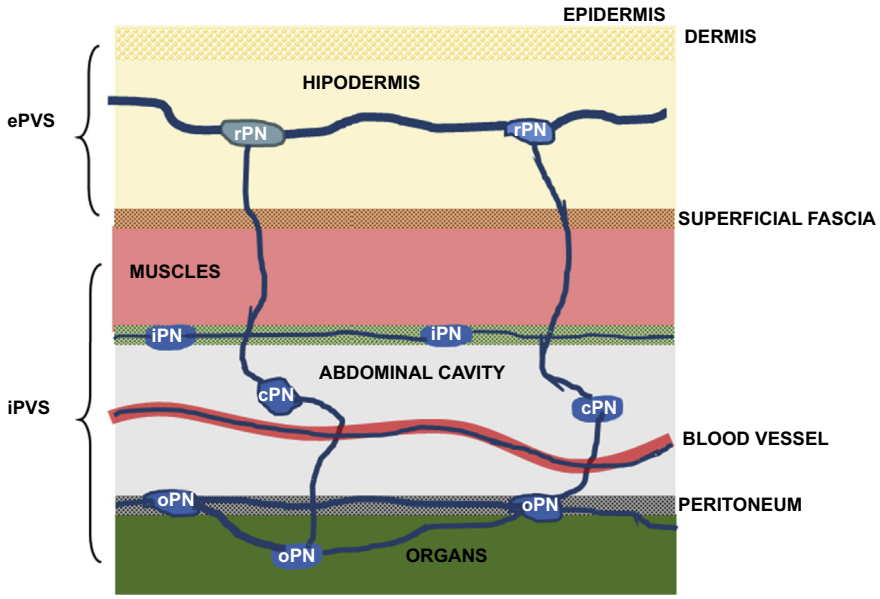

Figure 2 Topology and division of the PVS as proposed by Stefanov *et al* [38]. The division consists in external primo vascular system (ePVS) and internal primo vascular system (iPVS). Structures involved are the receiving primo nodes (rPNs), internal primo nodes (iPNs), communicating primo nodes (cPNs), and organic primo nodes (oPNs). Those nodes are connected by the primo nodes that are connected by the primo vessels (PVs), structures drawn in blue.

meridians [59] The hypothesis of NDS (PVS) being a path for signal transmission in acupuncture is based on the following.

4.2.2.1. Arrangement of the structures of the PVS

Acupuncture points are singularities appearing on the skin near to neurovascular bundles, neuromuscular attachments, or sensory nerve endings. Those points may reach the subcutaneous tissue that is above the muscle with interstitial space that include blood vessels, nerves, loose connective tissue, and superficial fascia and thus the rPNs that are connected to the PVs (Fig. 2). When electropuncture is made, the information is transmitted by electrical signals into the PVs by means of their excitable cells similar to the smooth muscles. Fletcher [60] proposed a new definition of acupuncture meridian in which it is hypothesized that the superficial PVS enclose the acupoints. Unfortunately it looks like the superficial PN and PVs are the less confirmed part of the PVS.

4.2.2.2. Histological and functional characteristics of those structures

(i) the existence for a number of cells (monocytes, eosinophils, mast cells and macrophages) related with inflammatory and immunologic responses in the Primo fluid of the organ surface primo vascular system;

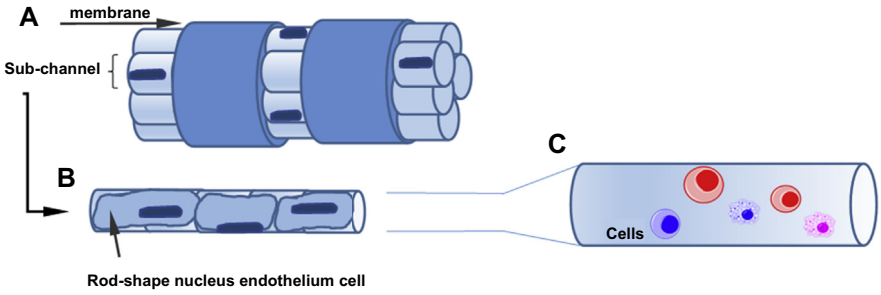

Figure 3 The Primo Vascular System (PVS). (A) Schematic representation of a primo vessel (PV). The membrane of the PV has high concentration of hyaluronic acid and consists of several subchannels. (B) A subchannel with an endothelium membrane with a rod-shaped nucleus cell. It is described also as having an adventitia that has connective tissue made of collagen. (C) The subchannels carry a liquid, the primo liquid, with cells, microcells, stem cells, and several substances such as hormones and proteins. The cells of the PVS show smooth-muscle Ca^{2+}-excitable cells that are related to the movement. Organ surface PVs and PNs have monocytes eosinophils, mast cells, and macrophages. PNs = primo nodes; PVS = primo vascular system. (Adapted from the study by Kang et al [56].).

(ii)The existence of chromaffin cells (similar to the neuroendocrine cells found in the medulla of the adrenal gland and in other ganglia of the sympathetic nervous) in the acupoints as well as in the organic PVS, able to secrete and to release adrenaline (epinephrine) and noradrenaline (norepinephrine) into the internal fluids [61] acting as an alternative endocrine catecholamine organ and thus as a hormone path;
(iii)The iPVS has main function in hematopoiesis;
(iv)The PVS as a network for the fusion and dispersion of eDNA microvesicles that would allow eDNA microvesicles to interact with one another, forming cell-like structures that would then been linked with immune system functions. The fusion of eDNA microvesicles is closely associated with recent research in the field of microvesicles, sometimes called exosomes or microparticles. Microvesicles have been shown to play a role in intercellular communication and regeneration of tissues (Fig. 3).

Regarding the way the signal is transmitted from the periphery to the organ where the therapeutic effect takes place, theories have been proposed such as the following:

(i) The introduction of a needle in the skin would induce mechanical and electrical stimuli and would act as antenna caption of external electromagnetic fields.
(ii) The PVs are surrounded by a membrane with high concentration of hyaluronic acid. Because of this, it has been theorized that hyaluronic acid may act as a biophoton carrier, which explains the instantaneous effects of needling in acupoints. A brief revision of state of the art concerning biophotons and biological structures is given in Section 4.3.
(iii) In a pathological situation, damaged cells send out signals and the PVS transmits the information through the PV fluid and provides the repair of the damaged cells. Those mechanisms imply important contributions from the nervous and cardiovascular systems, which are constituted by organs that have an extended net of PV vessels.
(iv) The PVS would work as an optical channel, and *qi* would be an electromagnetic standing wave. Speculations concerning the existence of a system of communication that sends messages to all organs based on electromagnetic signals have been made based in works of Rattemeyer et al [62]. that have suggested that conformational changes in DNA could be a source for biophoton emission. Accordingly, in the PVS, there are channels distributed all over the body and carrying DNA granules that connect the acupoints in the skin to the internal organs. The PVS would act as *cit*. "*an optical channel able to produce a coherent photon state capable of transmitting the information from outside to the inner body*". This theory would find its scientific basis on quantum communication [59] (See Section 4.3.1 for discussion of quantum coherence and quantum mechanisms in biological systems).

4.3. Biophotonic theory

Before proceeding with the discussion, it may be interesting to review the state of the art regarding the origin of the biophotons in the biological structures.

Biological tissues typically produce an observed radiant emittance in the infra-red, visible and ultraviolet wavelengths, ranging from 200 to 750 nm with low flux [63,64] between 10^{-17} and 10^{-23} W/cm^2. Biophotons are photons of the ultraviolet and low wavelength visible light range that are produced by a biological system as consequence of its metabolic processes. This low level of light has a much weaker intensity than the visible light produced by bioluminescence, but biophotons are detectable in cell cultures in the dark.

An acceptable hypothesis concerning the origin of biophotons is their emission during oxidative processes occurring in the cells [65], for instance, artificial sun light enhances those processes and also increases the emission of biophotons [66]. Some of the proposed physical mechanisms for biophoton production in cells are related to chemiexcitation due to the oxidative stress generated by reactive oxygen species (ROS) or action of catalytic enzymes such as peroxidases and lipoxygenases. Those biochemical reactions may lead to the formation of triplet excited species that release photons when returning to their fundamental state, as has been suggested by studies in which an increase of biophoton emission has been detected when a tissue is devoid of antioxidants [67]. The same effect may be reached when the amount of ROS in the cell is increased [68,69].

In addition to ROS, DNA has also been identified as a source of biophotons. Based on the fact that when ethidium bromide (EB), an agent that increases the unwinding (conformation) of DNA, was intercalated into the DNA, an increase in biophoton emission was measured, Popp et al [70]. suggested that biophoton emissions were strongly correlated to the unwinding of DNA and *cit*. "*that chromatin was one of the most essential sources of biophoton emission*". The ultraweak photon emission from living systems has found to present a high degree of coherence owing to its photon count statistics, its spectral distribution, and its decay behavior after exposure to light illumination and its transparency through optically thick materials [71].

4.3.1. Signal transmission based on quantum effects

Even though the emission of biophotons is nowadays accepted by biologists, biophotonic theory associated with neural conduction and cell intercommunication is just a theory whose biophysical basis will be here described, in a very simple manner, to permit the reader to make a positive judgment about its importance.

There are biological phenomena which cannot be understood and explained with recourse to molecular biology or conventional biological thinking: they are better explained by quantum effects such as those related with electronic and biophotonic coherent fields and tunneling.

In quantum mechanics, matter has wave-like properties. As such, elementary particles such as electrons and photons can act as wave functions and light waves. Waves, unlike matter, have properties such as diffraction, interference and superposition and tunneling.

The ability to interfere and diffract is related to coherence. When a number of particles are represented by a quantum pure state, they can be envisaged as a wave and they can superimpose their wave functions and give rise to coherent superimposition when they are in phase. Macroscopic scale quantum coherence leads to phenomena such as the laser, superconductivity and superfluidity. Tunnelling refers to the ability of a small mass particle to travel through energy barriers. Electrons have both wave and particle properties, so they have a low probability to pass through physical barriers as a wave without violating the laws of physics. Quantum tunneling is among the central nontrivial quantum effects in quantum biology. Here, it is important both as electron tunneling and proton tunneling. Electron tunneling is a key factor in many biochemical redox reactions (photosynthesis, cellular respiration) as well as enzymatic catalysis, while proton tunneling is a key factor in spontaneous mutation of DNA [72,73].

Studies show that long-distance electron transfers between redox centers through quantum tunneling plays important roles in enzymatic activity. For example, studies show that long-range electron tunneling in the order of 15-30 Å plays a role in redox reactions in enzymes of cellular respiration. Without quantum tunneling, organisms would not be able to convert energy quickly enough to sustain growth. Further research is needed to determine whether this specific tunneling is also coherent [74-76].

The question nowadays is open to determine whether communication based on coherence and tunneling can be also carried out by biophotons. As ultraweak radiation biophotons do not have energy enough to cross structures of high density and thickness, so their emission phenomena have been only observed on the skin, surface of isolated organs, plant leaves and roots, or cell cultures. Biophotons emerging from inner structures in the body may be not detectable from the outside owing to attenuation, but it is easy to accept that inner organs also produce biophotons as a result of their cellular oxidative metabolism.

Some hypotheses have considered the roles of biophotons that are released in internal organs, namely, in local cell communication and the state of biological tissues [77] Those suggestions were earlier made by Albrecht-Buehler [78] who conducted experiments with near-infrared—directing light onto cell-sized latex beads, which were situated near mouse fibroblast cells (connective tissue cells) and with elongated hamster cells. Some more recent studies conducted by Fels [79] confirm physical long-range cell-cell communication based on electromagnetic fields in the neighbor effect on induction or inhibition of cell growth in a population of the protozoan *Paramecium caudatum*, but hypotheses that biophotons facilitate a form of cellular communication are still under investigation, namely, concerning the clarification about the mechanisms that enable cells to distinguish signals sent by biophoton level of radiation from the other environment electromagnetic radiation.

5. Concluding remarks

In general, miscellaneous theories have been proposed in attempts to explain the working mechanisms underlying acupuncture practice.

Some are based on the classical theories of neural conduction that furnishes models explaining signal transduction and transmission based nociceptive reception, local neural active substances release, and stimulation of afferent fibers that are able to transmit the neural information to the central structures. The association of opoid neurotransmitter release during acupuncture has been proved in early 1970s. Studies of its effectiveness, at least in particular conditions such as chronic diseases and addictions, have been supported by many studies, but there are still experiences revealing contradictory results that justify the criticism on the part of the scientific community. The use of acupuncture in analgesia is the area where the practice is most accepted, although some recent studies concluded that its effectiveness was no higher than a placebo effect [80-82]. In any case, concerning analgesia, the neural conduction and gate control theory provide reasonably good models showing how acupuncture may work. Concerning the therapeutic effects on addiction control, psychosomatic disorders, and metabolic disorders, there is still much controversy about the effectiveness of treatments based on acupuncture. Nonetheless, it has been shown that the endogenous release of neurotransmitters promoted by acupuncture do not solely act in pain control: various types of opioid receptors are distributed differently within the central and peripheral nervous system, and opioidergic neurotransmission influences cardiovascular functions, thermoregulation, respiration, neuroendocrine functions, neuroimmune functions, food intake, sexual activity, aggressive locomotor behavior, as well as learning and memory.

Other theories are based on more recent studies that concern on new paths for supporting the signal transmission other that the nervous system, like Primo Vascular System (Hyaluronic Acid-rich Node and Duct System). Some theories state that conduction with the Hyaluronic Acid-rich Node and Duct System, is supported by positive holes in the hydration layer of collagen or cellular gap-junctions.

Another approach is related with conduction of information by biophotons. It is now well accepted that neural conduction theory is not satisfactory in explaining some complex capabilities of the human being, for instances, how brains think. Classical neural conduction implies the existence of a synaptic transmission with duration of at least 0.5 ms and transmission action potentials along an axon whose speed varies between 0.5 ms^{-1} and 120 ms^{-1}; thus, the transmission across thousands of synapses would take longer than the thinking process. As referred by Rahnama *et al.* [83], *"Synaptic transmission and axonal transfer of nerve impulses are too slow to organize coordinated activity in large areas of the central nervous system."* The same argument is used by those who suggest that signal transmission in acupuncture (*de qi* feeling) is too fast to be conducted by neurons in the classical manner.

Regarding thought processing, for instance, it has been advanced that the increase of speed on information transmission could be achieved by the use of biophotons combined to form a coherent pattern [84-86] by protein structures or DNA within the cells as part of its cytoskeleton. These thin tubes may be likened to optics fibers and are thought to transmit energy within a cell and between other cells by building junctions. In parallel, some authors claim that the PVS would work as an optical channel and *qi* would be an electromagnetic standing wave in which conformational changes in DNA could be a source for biophoton emission.

Those approaches, although based on reliable scientific studies, have been performed only by a few working groups, and so, by inheritance, their support and credibility is tarnished by lack of a high number of reports made by other researchers as well as the lack of periodic references in the most reliable journals. Those are arguments that support a wide community of skeptics that regard those theories as pseudoscience. In addition, theories that are based on difficult biophysics concepts, although sensible, are not introduced to medical readers in simple manners, and most of them are used as a foundation for other metaphysics thinking, such as quantum mysticism, that hinder and compromise the acceptance of some alternative practices by the medical and scientific community.

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Conflict of interest

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