

The Mechanism of Acupuncture - Beyond neurohumoral theory

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ABSTRACT

Acupuncture points and meridians have been discovered to have high electric conductance which is related to high density of gap junctions. Neurohumoral approach in acupuncture research was instrumental in establishing the scientific validity of acupuncture. However, it is largely descriptive with little prediction power.

It also has not been able to explain many observations in acupuncture. Based on the morphogenetic singularity theory, acupuncture points originate from the organizing centers in morphogenesis. This theory explains several long-standing puzzles in both developmental biology and acupuncture research, including the distribution and non-specific activation of organizing centers and acupuncture points, the high electric conductance of acupuncture points, the polarity effect of electroacupuncture and side effect profile of acupuncture, as well as the ontogeny, phylogeny and physiological function of the meridian system and chakra system.

Most of these have not been explained by any neurohumoral theory. In several 'prospective blind trials', main-stream biomedical researchers have confirmed its corollary on the role of singularity and separatrix in morphogenesis, the predictions on the high electric conductance and the high density of gap junction at the organizing centers. These advances have profound implications in biomedicine.

Physical characteristics of the acupuncture points and meridian system

According to the Standard Acupuncture Nomenclature proposed by the World Health Organization (WHO),[1] the meridian system in acupuncture consists of about 400 acupuncture points and 20 meridians connecting most of the points.

Since the 1950s, it has been discovered and confirmed by researchers in several countries with refined techniques [2] that most acupuncture points correspond to the high electrical conductance points on the body surface [3,4,5,6,7] and vice versa.[8] The high skin conductance of the meridian system is further supported by finding of high density of gap junctions at the epithelia of the acupuncture points.[9,10,11,12] Gap junctions are hexagonal protein complexes that form channels between adjacent cells.

It is well established in cell biology that gap junctions facilitate intercellular communication and increase electric conductivity. Acupuncture and meridian points have also been found to have higher temperature[13], higher metabolic rate and carbon dioxide release.[14]

The neurohumoral approach

In acupuncture analgesia, the peripheral nervous system has been shown to be crucial in mediating the effect. The analgesia can be abolished if the acupuncture site

is affected by postherpetic neuralgia[15] or injection of local anesthetics[16].

In other effects of acupuncture such as anti-hyperglycemic effects, studies have shown that local blockade of peripheral nerves or denervation did not interfere with the acupuncture effect[17]. In the 70s, the relation between cerebral cortex and acupuncture alteration of visceral function was explored by examining the cortical evoked potentials, single unit discharges and neurochemistry associated with acupuncture.

These studies brought forth the Meridian-Cortex-Viscera correlation hypothesis[18] which states that: 1. The meridian system is an independent system connected via the nervous system to the cerebral cortex. 2. It acts through neurohumoral mechanisms[19]. Recently, a more generalized acupoint-brain-organ model was proposed that acupuncture first stimulates the corresponding brain cortex via the nervous system, thereby controlling the chemical or hormone release to the disordered organs for treatment.[20]

In the mid-70s, the discovery of endorphin induction in acupuncture analgesia and its blockade by naloxone played a key role in establishing the validity of acupuncture in main-stream science.[21,22] Animals which respond poorly to acupuncture analgesia can be rendered good responders by treatment with D-phenylalanine which inhibits the degradation of met-enkephalin[23].

A close relation between acupuncture and nervous system is also indicated by the large overlap between acupuncture points and trigger points - points of maximum tenderness in myofascial pain syndrome[24]. These results have led some practitioners to believe that the meridian system as described in the classic acupuncture literature does not exist and that all the effects of acupuncture are mediated through nervous system.[25,26] Other scholars regard the neurally mediated acupuncture phenomena as "not the central core of the mechanism of acupuncture".[27] The current neurohumoral theory of acupuncture has been mostly descriptive with little prediction power. It has difficulty in explaining a number of phenomena in acupuncture:

1. The distribution of acupuncture points: For example, an auricle has no important nerves or blood vessels and no significant physiological function other than sound collection, it nevertheless has the highest density of acupuncture points. According to the WHO, 43 auricular points have proven therapeutic value, which consist of 10% of the acupuncture points of the whole body.

2. The non-specific activation of acupuncture points: Each type of nerve usually responds to certain specific modalities of stimuli. Therapeutic effect of acupuncture can be achieved by a variety of stimuli[28,29] including needling, temperature variation, laser[30], ultrasound, vacuum and pressure.

3. The bi-directional regulation effect of acupuncture: Conventional nerve stimulation usually result in uni-directional effect. For example, vagal stimulation slows down heart rate. Opioids inhibits gut motility. However, acupuncture at PC6 accelerates bradycardia and decelerates tachycardia. Acupuncture at ST36 suppresses hyperfunction (as in diarrhea) and stimulates hypofunction (as in constipation) of the gut motility.[31] Therefore, proper use of acupuncture causes few side effects[32,33,34,35] as demonstrated in randomized controlled trials[36,37], unlike most of the conventional nerve-stimulation therapies.

The morphogenetic singularity theory

The morphogenetic singularity theory[38] developed over the last 2 decades is compatible with the neurohumoral findings of acupuncture effect and also can explain many phenomena in acupuncture beyond the neurohumoral theory.

Acupuncture points are singular points in surface bioelectric field

Epithelia usually maintain a 30-100 mV voltage difference across themselves.[39] This voltage is the potential difference across cell layers, not membrane potential. An acupuncture point which has high density of gap junctions and local maximum electric conductance will also have locally maximum electric current density – a converging point of surface current.

It is a singular point of abrupt change in electric current flow. A singular point is a point of discontinuity as defined in mathematics. It indicates abrupt transition from one state to another. Small perturbations around singular points can have decisive effects on a system. As James Maxwell observed: "Every existence above certain rank has its singular points ... At these points, influence whose physical magnitude is too small to be taken account of by a finite being, may produce results of the greatest importance." [40]

The pattern of electromagnetic field on the human scalp mapped by SQUID (Superconducting QUantum Interference Device)[41] shows that the acupuncture point GV20 Baihui is a singular point at the surface magnetic field where the surface magnetic flux trajectories converge and enter the inside of the body. (Dr. Magnus Lou, personal communication) The Governor Vessel is a converging pathway of magnetic flux on the scalp and also a separatrix which divides the surface magnetic field into two symmetrical domains of different flow directions.

A separatrix is a trajectory or boundary between spatial domains in which other trajectories have different behavior.[42] Morphologically, the Governor Vessel is also the axis of symmetry on the scalp. This pattern is consistent with the pattern of the meridian system, but different from the distribution of any major nerve, lymphatic or blood vessel on the scalp. The morphogenetic singularity theory suggests that the meridian system is related to the bioelectric field in morphogenesis and growth control.[38]

The role of electric field in growth control and morphogenesis

A variety of cells are sensitive to electric fields of physiological strength.[43] Somite fibroblasts migrate to the negative pole in a voltage gradient as small as 7 mV/mm.[44] Asymmetric calcium influx is crucial in the migration which can be blocked or even reversed by certain calcium channel blockers and ionophores.[45]

In most cases, there is enhanced cell growth toward cathode and reduced cell growth toward anode in electric fields of physiological strength.[46,47] Fast growing cells

tend to have relative negative polarity. This polarity is due to the increased negative membrane potential generated by the mitochondria at high rate of energy metabolism.[48] Imposed electric fields can cause polarization of mouse blastomeres,[49] reversal of anterior-posterior polarity[50] and dorsal-ventral polarity[51] in lower animal morphogenesis.

Organizing centers have high electric conductance

In development, the fate of a larger region is frequently controlled by a small group of cells, which is termed an organizing center.[52] Organizing centers are the high electric conductance points on the body surface:[38]

The amphibian blastopore, a classic organizing center, has high electric conductance and current density.[53] Similar phenomena have also been observed in higher vertebrates.[54] The high conductance phenomenon is further supported by the finding of high density of gap junctions at the sites of organizing centers.[55,56,57,58] At the macroscopic level, organizing centers are singular points in the morphogen gradient and electromagnetic field.38 Disruption of electric field at the organizing center can cause malformation.[53]

Change of electric activity at the organizing centers correlates with signal transduction and can precede morphologic change.[59,60] For example, in amphibians, an outward current can be detected at the site of a future limb bud (an organizing center) several days before the first cell growth.[61]

Acupuncture points originate from organizing centers.

Both acupuncture points and organizing centers have high electric conductance, current density, high density of gap junctions and can be activated by nonspecific stimuli. Therapeutic effect of acupuncture can be achieved by a variety of stimuli as mentioned above. Similarly, morphogenesis of organizing centers can be induced by various stimuli such as mechanical injury and injection of nonspecific chemicals.[52,62]

Meridian – Separatrix - Boundary

At early stages of embryogenesis, gap junction mediated cell-cell communication is usually diffusely distributed which results in the entire embryo becoming linked as a syncytium. As development progresses, gap junctions become restricted at discrete boundaries, leading to the subdivision of the embryo into communication compartment domains.[63]

These boundaries are major pathways of bioelectric currents and divide the body into domains of different electric current directions. Separatrices can be folds on the surface or boundaries between different structures and often connect singular points.[38,64] Meridians are separatrices[38] and related to a under-differentiated,[9] interconnected cellular network that regulates growth and physiology. The attributes of separatrix is consistent with the observation in the Inner Classic (Nei Jing) that meridians lie at the boundaries between different muscles.

For example, part of the lung meridian runs along the borders of biceps and brachioradialis. Part of pericardium meridian runs between palmaris longus and flexor carpi radialis. Part of gallbladder meridian runs between sternocleidomastoid and trapezius. Trigger points also tend to locate at the boundaries of muscles.[65] The Governor Vessel and the Conception Vessel are the axis of symmetry of the body surface and the boundaries of many different structures.

They are also regarded as the convergence of all meridians in traditional acupuncture. In consistence with the under-differentiation of the meridians, it has been observed that the most apical part of folds remain undifferentiated in morphogenesis,⁶⁶including organizing centers such as apical ectodermal ridge.[67]

Why do auricles have the highest density of acupuncture points?

The distribution of acupuncture points and organizing centers is closely related to the morphology of the organism. For example, the auricle, which has the most complex surface morphology, also has the highest density of acupuncture points.

Although an auricle has no important nerves or blood vessels and no significant physiological function other than sound collection, its morphology is one of the most sensitive signs of malformations in other organs. Auricular malformation has been observed in Turner syndrome, Potter syndrome, Treacher-Collins syndrome, Patau syndrome, Edwards syndrome, Noonan syndrome, maternal diabetes, atherosclerosis,[68] Goldenharr syndrome, Beckwith syndrome, DiGeorge syndrome, Cri-du-chat syndrome and fragile X syndrome.

It is recommended in a standard textbook of pediatrics that any auricular anomaly should initiate a search for malformations in other parts of the body.[69]

Based on the phase gradient model in developmental biology, [38,70] many organizing centers are at the extreme points of curvature on the body surface such as the locally most convex points (e.g., the apical ectodermal ridge and other growth tips) or concave points (e.g., the zone of polarizing activity).

Similarly, almost all the extreme points of the body surface curvature are acupuncture points, for example, the convex points include EX-UE11 Shixuan, EX-LE12 Qiduan, ST17 Ruzhong, ST42 Chongyang, ST45 Lidui, SP1 Yinbai, SP10 Xuehai, GV25 Suliao, EX-HN3 Yintang ... The concave points include CV17 Danzhong, KI1 Yongquan, LI5 Yangxi, LU 5 Chize, LU7 Lieque, LU8 Jingqu, LU10 Yuji, SI19 Tinggong, TE21 Ermen, GB20 Fengchi, GB30 Huantiao, BL40 Weizhong, HT1 Jiquan, SI18 Quanliao, BL1 Jingming, CV8 Shenque, ST35 Dubi ...

The role of the meridian system in evolution and physiology

In ontogeny, the development of organizing centers in the growth control system precedes the development of the nervous system and other physiological systems. The formation and maintenance of all the physiological systems are directly dependent on the activity of the growth control system.

As the individual embryonic development recapitulates the evolution of the

species,(ontogeny recapitulates phylogeny) the evolutionary origin of the meridian system as an intercellular signal transduction system of growth control is likely to have preceded all the other physiological systems, including the nervous system. Its genetic blueprint might have served as a template from which the newer systems evolved. Consequently, it overlaps and interacts with other systems but is not simply part of the nervous system.

The meridian signal transduction is embedded in the activity of the function-based physiological systems. The regulation of many neural, circulatory or immune processes is through growth control mechanisms such as hypertrophy, hyperplasia, atrophy, apoptosis with shared messenger molecules and common signal transduction pathways involving growth control genes such as proto-oncogenes.[71,72,73,74,75] Acupuncture also induces the expression of proto-oncogene c-fos. [76,77] Many "non-excitables" cells have shown electrochemical oscillation, coupling, long range intercellular communication [60,78,79] and can participate in the meridian signal transduction.

A unified basis of meridian system and chakra system

Based on the morphogenetic singularity theory, the distribution of meridian system is related to both internal and external structures, and not solely determined by nerves, muscles or blood vessels. The distribution is a result of morphogenesis.

Therefore, acupuncture points which are not at obvious extreme points of surface curvature or meridians which are not at obvious surface boundaries may be vestigial or more related to internal structures. The under-differentiated, inter-connected cellular network is not limited to the body surface. The distribution pattern of a certain type of primary tumors reflects the distribution of its normal counterpart.

For example, the distribution of primary pheochromocytoma reflects the distribution of normal sympathetic ganglion cells. One type of the least differentiated cells is germ cell. The germ cell tumors [80,81] have a midline and para-axial distribution pattern which spans from the sacrococcygeal region, through anterior mediastinum, tongue, nasopharynx, to pineal gland. It appears to concentrate at 7 locations: sacrococcygeal region, gonads, retroperitoneum, thymus,[82] thyroid, [83] suprasellar region, and pineal gland.[84] The pattern resembles the chakra system used in yoga and acupuncture,[85] suggesting the existence of under-differentiated cells which may be highly inter-connected in a normal state as part of the "inner meridian system" and provide important regulatory functions.[86]

Mechanism of meridian system based diagnosis and therapy

As the electrical conductance of organizing centers varies with morphogenesis, the conductance of acupuncture points also varies and correlates with physiological change³ and pathogenesis.[87,88] The fact that the change in electric field precedes morphologic change⁶¹ and manipulation of the electric field can affect the change[89] may shed light on the diagnosis[90] and treatment of many diseases.

According to the theory,[38] the network of organizing centers retain its regulatory function through high levels of intercellular communication correlated with relatively low levels of cell differentiation after embryonic development. This prediction is

consistent with the finding that the high electric conductance persists at the organizing centers after early embryogenesis.[91] The organizing centers may communicate with other parts of the body to maintain proper forms and functions.

Gap junctional communication has been shown to play a crucial role in morphogenesis.[92] The gap junction genes can also behave as classical tumor suppressor genes both in culture and in animal tests in restoring growth regulatory properties to metastatic cancer cells.[93] An anomaly inside the organizing center network may be detected by measuring the electrical parameters of some points on its surface at the early signal transduction stage and treated by manipulation of the interconnected organizing centers.

The activation of organizing centers is likely to be involved in the restoration of proper form and function in wound healing and stress response. Acupuncture can speed up the wound healing process [94] and cause an exaggerated systemic wound healing and stress response.[95,96]

The response can include excessive release of endorphin which stimulates epithelial cell growth[97] as well as analgesia. Other neuro-humoral factors induced by acupuncture such as serotonin[98] and ACTH[99] also have growth-control effects.[100]

A principle in electroacupuncture is that positive (anode) pulse stimulation of a point inhibits its corresponding function while negative (cathode) pulse stimulation enhances the function.[101] This polarity effect is similar to the finding that cell growth is enhanced toward cathode and reduced toward anode,[46,47] consistent with the theory that the mechanism underlying acupuncture overlaps with that of growth control.

Why does acupuncture has normalizing effect and few side effects?

In acupuncture, the often nonspecific perturbation at singular points (acupuncture points) may not directly antagonize a pathological process but may indirectly adjust the process and restore normal function by activating the network of organizing centers in the organism. The activation of the self-organizing activity is less likely to cause the side effects resulted from directly antagonizing a pathological process which often overlap with other normal and beneficial physiological processes.

Summary

The morphogenetic singularity theory outlines the common ground shared among meridian system, chakra system and modern sciences. It is compatible with the findings from neurohumoral studies. It explains several long-standing puzzles in both developmental biology and acupuncture research.

These include the distribution of meridian system, chakra system and germ cell tumors, the non-specific activation of acupuncture points and organizing centers, the high electric conductance of acupuncture points, the polarity effect of electroacupuncture and side effect profile of acupuncture, as well as the ontogeny, phylogeny and physiological function of the meridian system.

Most of these have not been explained by any neurohumoral theory. In several 'prospective blind trials', [53,55,56,57,65] main-stream biomedical researchers, who were unaware of the theory, confirmed its corollary on the role of singularity and separatrix in morphogenesis, and its predictions of the high electrical conductance and high density of gap junctions at the organizing centers such as blastopore and zone of polarizing activity.

Techniques involving the stimulation of the meridian system such as acupuncture and qigong [102,103] may activate the self-organizing system of an organism and improve its structure and function at a more fundamental level than symptomatic relief. Development of these techniques may enable the diagnosis and treatment of a pathologic process at the early signal transduction stage prior to the anatomical or morphological change.

Prospects

The advances reviewed above have broad implications in biomedicine beyond acupuncture. The current stage of research on acupuncture and medicine is analogous to that of physics in early 19th century – at the transition from Newtonian mechanics to electromagnetics. Many questions remain unanswered.

More spectacular advances similar to that of relativity and quantum physics may await us in the next century and will depend on the further development of meridian "electromagnetics". Many other areas such as psychophysiology, chronobiology, [104] and pulse analysis [105] related to the meridian system are awaiting more rigorous studies. Many details of the current theories remain to be clarified and tested.

Besides the neurohumoral studies, the following directions of research are likely to be important in further understanding acupuncture and meridian system:

1. Mapping of meridian system and the dynamics of its electromagnetic field with high resolution techniques such as SQUID.
2. The relation between the physical parameters of meridian system and various pathological or physiological changes, including changes during acupuncture and qigong practice.
3. Develop acupuncture related techniques of early diagnosis and treatment and establish their cost-effectiveness.
4. Clarify the role of meridian system in morphogenesis and growth control.
5. Cell differentiation and signal transduction in meridian system.
6. Mapping the body surface curvature through embryonic development with imaging techniques and study its relation with meridian system.