

An inspiration to the studies on mechanisms of acupuncture and moxibustion action derived from 2021 Nobel Prize in Physiology or Medicine

Yi Guo^{1,2,3,*}, Yongming Li⁴, Tianle Xu⁵, Michael Xi Zhu⁶, Zhifang Xu^{1,3,7}, Baomin Dou¹, Yanwei Li¹, Zhihan Chen¹

Abstract

The editorial board of *Acupuncture and Herbal Medicine* recently convened an academic seminar with a focus on studies regarding the mechanisms mediating acupuncture efficacy and moxibustion action inspired by the 2021 Nobel Prize in Physiology or Medicine. Specifically, Professor Bailong Xiao introduced the Nobel Prize for research on the mechanically activated Piezo ion channel, evaluating the structure of the Piezo channel and its physiological and pathological functions, and proposed a possible role for the Piezo channel in acupuncture mechanical stimulation. Professor Michael Xi Zhu introduced the discovery of the transient receptor potential (TRP) family, reporting that the therapeutic effects of Chinese medicine and acupuncture may be achieved *via* the TRP family, and that information regarding associations between the meridian and lymphatic systems may have important research and medical value. In addition, Professor Tianle Xu reviewed the history of ion channel research, particularly the physiological and pharmacological effects of non-classical ion channels (eg, the acid sensing ion channel family) and pointed out that the characterization and neural circuits of acupuncture *deqi* manipulation are important for elucidating the mechanisms of acupuncture actions. Professor Yongming Li similarly proposed that the 2021 Nobel Prize may open the door to disclosing the histological basis of acupuncture and moxibustion and analyzing the main scientific concerns regarding the clinical translation of acupuncture and moxibustion from basic to translational research. Finally, Professor Yi Guo summarized the study progress of the acupoint microenvironment induced by acupuncture over the course of nearly 30 years and put forward the hypothesis that acupuncture may initiate the physical-chemical coupling network by activating ion channel receptors in acupoints *via* physical and mechanical stimulation. Therefore, we conclude that a primary achievement of the 2021 Nobel Prize in Physiology or Medicine is in helping interpret how acupuncture and moxibustion adjust homeostasis (ie, by activating mechanical and thermal sensation), which is conducive to validating and promoting the clinical efficacy of acupuncture modalities.

Keywords: 2021 Nobel Prize in Physiology or Medicine, Acupuncture, Ion channel, Moxibustion, Piezo, TRPV1

Introduction

The 2021 Nobel Prize in Physiology or Medicine was announced on October 4, 2021. Professors David Julius and Ardem Patapoutian were awarded the Prize for the

discovery of a temperature sensor (transient receptor potential cation channel subfamily V member 1, TRPV1) and a tactile sensor (termed Piezo2). Hence, neuroscience research has once again attracted great attention from the academic community and the public at large. TRPV1 is known to be an important temperature sensor, and its discovery paves the way to uncovering other critical temperature receptors. And the Piezo is a new mechanosensitive ion channel that responds to mechanical stimulation of the skin and viscera. These groundbreaking discoveries allow for a better understanding of how heat, cold, and mechanical forces trigger nerve impulses for the purpose of sensing and adapting to the world around us. The 2021 Nobel Prize in Physiology or Medicine opens the door for research on how precisely acupuncture and moxibustion works. Specifically, acupuncture and moxibustion are thought to exert their respective impacts through mechanical and temperature stimulation in order to achieve effective disease treatment as well as the maintenance of good health. However, there is currently no clear scientific explanation of how these physical stimulations induce biological actions. These are critically important scientific questions in acupuncture and moxibustion research.

A recent symposium on the findings of associated research following the 2021 Nobel Prize in Physiology or Medicine was sponsored by the editorial board of *Acupuncture and Herbal Medicine* and organized by the Research Center of Experimental Acupuncture Science at Tianjin University of Traditional Chinese Medicine.

Yi Guo, Yongming Li, Tianle Xu, Michael Xi Zhu, Zhifang Xu, Baomin Dou, Yanwei Li, and Zhihan Chen contributed equally to this study.

¹ Research Center of Experimental Acupuncture Science, Tianjin University of Traditional Chinese Medicine, Tianjin, China; ² School of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin, China; ³ National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin, China; ⁴ American Traditional Chinese Medicine Society, New York, NY, USA; ⁵ Collaborative Innovation Center for Brain Science, Department of Anatomy and Physiology, Shanghai Jiao Tong University School of Medicine, Shanghai, China; ⁶ Department of Integrative Biology and Pharmacology, The University of Texas Health Science Center at Houston, Houston, TX, USA; ⁷ School of Acupuncture & Moxibustion and Tuina, Tianjin University of Traditional Chinese Medicine, Tianjin, China

* Corresponding author. Yi Guo, School of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China, E-mail: guoyi_168@163.com.

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The symposium focused on mechanisms mediating acupuncture efficacy as well as moxibustion. Five renowned experts in the field of ion channel and acupuncture research were invited to give the keynote speeches, including Professor Bailong Xiao from Tsinghua University, Professor Michael Xi Zhu from the University of Texas, Professor Tianle Xu from Shanghai Jiao Tong University, Professor Yongming Li from American Traditional Chinese Medicine Society, and Professor Yi Guo from Tianjin University of Traditional Chinese Medicine. This seminar aimed to accelerate knowledge regarding the mechanisms mediating acupuncture, and moxibustion and to conduct rigorous empirical research validating and promoting the clinical efficacy of acupuncture for a range of diseases.

The discovery of the Piezo family and the resulting impact on acupuncture research

Professor Bailong Xiao at Tsinghua University devoted his session to exploring how mammals, including humans, perceive mechanical stimuli, and likewise focused on identifying and characterizing temperature-activated and mechanically activated ion channels (eg, Piezo channels) as well as gaining a better understanding of the molecular and cellular mechanisms mediating the sense of touch, pain, and mechano-transduction in other biological systems. He likewise focused on his efforts to develop novel medicine approaches by targeting these ion channels.

Professor Xiao presented a speech entitled “How do we perceive things”? He shared his postdoctoral research experience at the Scripps Research Institute, Professor Ardem Patapoutian Lab. Professor Patapoutian was one of the winners of the Nobel Prize in Physiology or Medicine in 2021. Professor Xiao participated in and witnessed the discovery of the mechanically-sensitive Piezo ion channels.

At that time, the TRP family had already been discovered and many breakthroughs had been made in delineating molecular receptors for temperature perception. However, the molecular mechanisms mediating mechanical force perception remained unsolved. In the absence of high-throughput screening, the Patapoutian laboratory applied mechanical force stimulation to single cells using electrophysiological techniques and found that N2A cell lines could generate inward current in response to mechanical force. RNA profiling was then implemented to identify more than 500 candidate genes in N2A cells and to knockdown the target genes one by one. Finally, researchers landed on the 72nd candidate gene, Piezo1, which determines the cell’s mechanically sensitive current. The second protein identified according to its homology with Piezo1 was termed Piezo2^[1].

Professor Xiao introduced a 3D structural analysis of Piezo channels. Mouse Piezo2 is a three-bladed, propeller-like trimer comprising 114 transmembrane helices (38 helices per protomer)^[2]. Transmembrane helix 136 (TM136) is folded into nine tandem units of four transmembrane helices each to form these unusual non-planar blades^[3]. The three blades are collectively curved into a nano-dome 28 nm in diameter and 10 nm in depth, with an extracellular cap-like structure embedded in the center and a 9 nm-long intracellular beam connecting to the central pore. TM38 and the C-terminal domain are

surrounded by the anchor domain and by TM37 and enclose the central pore with both transmembrane and cytoplasmic constriction sites^[4]. The molecular mechanism mediating the Piezo channel response to mechanical force is a mechanical force extruding from the cell membrane. More specifically, Piezo’s “blade” structure drives the “central plug” structure inside the cell membrane to open the central pore. Cations such as calcium and sodium enter the cell to cause depolarization. The excitation of sensory neurons leads to the generation of touch and ontology^[5].

Through nearly ten years of research, Professor Xiao and his group discovered that Piezo channels undertake a wide range of physiological and pathological functions. Piezo1 is widely expressed in many cells and tissues, including erythrocytes, the endothelium, smooth muscle, and cardiomyocytes, and is involved in sensing the dramatic mechanical changes caused by cardiac contraction and relaxation, thus regulating cardiac homeostasis^[6]. Bones feel gravity because Piezo1 is expressed in osteoblasts; Piezo1 is likewise involved in bone formation and remodeling^[7]. Piezo2 is expressed in sensory neurons and mediates touch, proprioception^[8], viscera, mechanical force perception, and tactile pain^[9-10]. Piezo channels likewise mediate the genesis of mutations in human genetic disease^[10], such as gain-of-function mutations in Piezo1 are associated with dehydrated hereditary stomatocytosis, while loss-of-function mutations cause lymphatic dysplasia. Gain-of-function mutations in Piezo2 are linked with distal arthrogryposis, Gordon syndrome, and Marden Walker syndrome, whereas loss-of-function mutations lead to scoliosis, respiration defects, and an impaired sensation of gentle touch, tactile pain, proprioception, and dysfunction of bladder control. Therefore, Piezo gene mutations can directly lead to human genetic disease and are likewise important and novel drug targets^[9-12].

Finally, Professor Xiao mentioned that Piezo channels on sensory neurons may be involved in the mechanical stimulation of acupuncture. Both positive extrusion pressure and negative suction force can activate Piezo channels. Traditional acupuncture manipulation, including lifting and twisting, produce different forms of force on the body. Whether these forces activate different Piezo channels is worthy of further study. At the same time, some studies have confirmed that Piezo channels are involved in analgesia, and thus corresponding small-molecule analgesics are likewise under development. Whether the Piezo channel plays a corresponding role in acupuncture analgesia is worthy of thorough study.

Discovery of the TRP ion channel and its impact on acupuncture research

Professor Michael Xi Zhu is a tenure-track professor at The University of Texas Health Science Center in Houston, TX. His research interests include several aspects of cell signaling, especially those involving heterotrimeric G proteins as well as ion channels that affect Ca²⁺ signaling. His main scientific contributions include the identification and characterization of multiple transient receptor potential canonical (TRPC) channels in mammalian species and the determination of the molecular identity of endolysosomal Ca²⁺ release channels activated by the Ca²⁺ mobilizing messenger, nicotinic acid adenosine dinucleotide-phosphate (NAADP).

Professor Zhu presented a speech entitled “Circuits, acupuncture, herbal medicine, and TRP channels”. First, he introduced relevant information on the discovery and physiological functions of TRPV1. Specifically, it was known as early as the late 1990s that capsaicin can activate nerve cells, thereby causing pain sensations. However, the mechanisms through which capsaicin exerts its effects were unknown. A painstaking search led by Professor David Julius identified a single gene that encodes sensitivity to capsaicin; later studies showed that this gene encodes a new ion channel protein, the capsaicin receptor^[13]. Due to their homology with the transient receptor potential (TRP) family, capsaicin and other ligands contain a vanillic acid structure known as TRPV1. Thus far, at least six subtypes of the TRPV family have been found, including TRPV1–6, TRPV1–4 (a heat sensitive ion channel), and TRPV5–6 (a calcium ion channel with high selectivity)^[14].

TRPV1 is an important temperature sensor that can be activated by a variety of physicochemical factors, including capsaicin and other vanillic acid compounds (eg, resiniferatoxin), thermal stimulation (ie, temperature >43°C), acidity (pH < 6.0), ethanol, reactive oxygen species, and hydrogen sulfide^[15]. TRPV1 can be activated directly or indirectly by a variety of neuroinflammatory and endogenous inflammatory mediators, such as bradykinin, substance P, prostaglandin, lipid peroxides, and adenosine triphosphate (ATP), nerve growth factor, and calcitonin gene-associated peptides. When TRPV1 is activated, a cationic influx of Ca²⁺ and Na⁺ can be induced; Ca²⁺ has selective specificity (approximately 5 times to 10 times that of other cations), leading to higher concentration of Ca²⁺ and corresponding physiological and pathological changes. TRPV1 is demonstrated to be involved in pain, inflammation, itching, hearing, taste, apoptosis, and other physiological and pathological processes *in vivo* studies^[16].

Finally, Professor Zhu discussed the relationship of ion channels with Chinese herbal medicine and acupuncture. In traditional Chinese medicine (TCM), the five tastes are defined as acid, bitter, sweet, hot, and salty. Professor Zhu brought up the question of how different tastes are mediated *via* different ion receptors. For example, spicy herbs (eg, ginger, mint, perilla) can make the body sweat and reduce fever. However, it is unknown whether there is a general correlation between spicy herbs and the TRP channel. It has been found that extracellular calcium ion concentrations are enriched after acupuncture stimulation, and that the calcium ion antagonists may influence the curative effects of acupuncture. Because increased extracellular calcium levels can be activated *via* calcium receptors, and TRP receptors are located downstream of the calcium receptor, whether calcium levels or TRP receptor activity induced by calcium receptors mediates acupuncture effects is worthy of in-depth study.

In 2009, Professor Zhu, in collaboration with scientists from Germany and England, found that smooth muscle in the gastrointestinal tract expresses TRPC, which can in turn mediate vagus nerve-derived acetylcholine to promote gastrointestinal peristalsis^[17]. Therefore, whether acupuncture at the ST36 site activates the vagus nerve or the parasympathetic nerve through ion channels with the effects of regulating visceral activity is likewise worthy of comprehensive study. In addition, Professor Zhu speculated that associations between the meridian and

lymphatic systems may be important to explaining the meridian essence.

The researches on the non-classical ion channel family and its impact on acupuncture research

Professor Tianle Xu is the Head of the Department of Anatomy and Physiology at the School of Medicine at Shanghai Jiao Tong University, as well as the Director of the Children’s Brain Science Center at the National Children’s Medical Center in Shanghai. He is committed to the study of physiological mechanisms and targets with respect to brain diseases, ion channels, neural circuits, learning, memory, and associated neurologic disease.

In his speech entitled “Ion channels and sensory physiology – implications from research on temperature and touch mechanisms”. Professor Xu reviewed the history of ion channel research, from the early discovery of classic ion channels (eg, sodium, potassium, and calcium channels), to the discoveries of the temperature receptor TRPV1, the tactile sensor Piezo, and other non-classical ion channels. Ion channel research is typically an interdisciplinary subject involving many fields (eg, neuroscience, pharmacy, proteomics). Chinese scientists have made many achievements in this field, such as contributions to elucidating the structure, function, and pharmacology of Piezo1/2 (Professor Bailong Xiao), and fine structural analyses of voltage-gated ion channels (Professor Ning Yan). Professor Xu and his group are likewise focused on research regarding the non-classical ion channel acid sensing ion channel (ASIC) family with respect to interactive/collaborative effects, gating ligand diversity, diversified characteristics, signal transduction mechanisms, and neural circuits in perception, learning, and memory.

In his speech, Professor Xu mentioned that the 2021 Nobel Prize has helped advance the scientific community’s understanding of touch and temperature sensation, with implications with respect to three primary research directions. First, sensory perception has always been at the forefront of brain science research. People subjectively attach much less importance to tactile sense than to vision, hearing, and smell. However, a tactile sense is of great significance to all human beings. Human beings use touch to not only perceive the external world, but also to interact with the world, communicate with other people, and build relationships. Touch is the earliest and most basic sense developed by the human body, and it is also the most widely distributed and complex sensory system in the human body^[18]. The body can sense temperature through the TRP channel^[19–20]. There are many TRP subtypes, and different subtypes can distinguish different temperatures. For example, TRPV1, TRPV2, and TRPV3 are heat receptors, while TRPM8 is a cold receptor^[13,15,21]. The molecular mechanisms mediating tactile and temperature perception through relevant ion channels have not been fully explained, and some non-classic ion channels likewise necessitate additional study. Second, abnormal sense perception may be an early warning sign and a common symptom of major diseases. For example, some patients display olfactory dysfunction in the early or later stages of neurodegenerative disease. Additionally, patients with autism can present with abnormal sensations of feeling, touch, and pain, and COVID-19 patients usually show a loss of taste and smell, paresthesia, visual impairment, social isolation, affective

disorders, and so on^[22–23]. However, the pathogenesis mediating these diverse effects is still unclear, thus presenting a major challenge with respect to future research^[24]. Third, there are currently many sensory therapies available, including visual and auditory interventions, and basic research regarding sensory perception is important for the development of effective sensory therapy modalities.

Professor Xu also discussed the impact of the 2021 Nobel Prize in terms of informing the study of mechanisms mediating acupuncture effects and efficacy. First, these mechanisms are complex, involving the nervous, immune, and endocrine systems. TRP ion channels, Piezo ion channels, ASICs, and glia-associated ATP receptors may each play important roles in the initiation of the acupuncture effect. Second, differing acupuncture manipulation and intensity may activate different ion channels (receptors) and may differentially activate neural circuits, hence achieving diverse effects^[19]. Therefore, elucidating the neural mechanisms of acupuncture treatment (from ion channels to neural circuits) is of critical importance. Finally, *deqi* is a key factor mediating the therapeutic effects of acupuncture. Specifically, the sensation of sour taste, numbness, heaviness, and distention will be perceived with various acupuncture procedures; the functional heterogeneity of sensory nerves depends on different ion channels as well as combined effects of ion channels^[25]. Non-classical ion channels may play corresponding roles in *deqi* manipulation induced by acupuncture. Therefore, it is of great significance to elucidate the objective characteristics and neural circuits relevant to *deqi* to elucidate the effective mechanisms mediating acupuncture actions.

Finally, Professor Xu mentioned that ion channels and neural circuits have been the cornerstones of brain science research for more than 100 years. It has been suggested that, according to the principle of “intersection, integration, cooperation and innovation”, it is advisable to form a large-scale and organized science research team. This team will eventually become an important force for generating immense progress in the mechanistic study of acupuncture efficacy and moxibustion action.

The 2021 Nobel Prize and the histological basis of acupuncture

Dr. Yongming Li, President of the American Traditional Chinese Medicine Society, studied at the University of Illinois at Urbana-Champaign and formerly worked at the Picower Medical Research Institute, where he was engaged in dermatological diagnoses and clinical research with respect to Chinese acupuncture and moxibustion.

In his report entitled “Implications of the 2021 Nobel Prize for acupuncture research”, Professor Li mentioned that, for the past 50 years, research on the mechanisms mediating acupuncture efficacy has focused on the effects of acupuncture on the central nervous system (ie, changes in enkephalins and associated neural circuits). However, there are still many unknown phenomena and therapeutic effects of acupuncture in the skin and other surrounding tissues that currently lack a clear scientific explanation^[26]. An important reason is that there is insufficient knowledge regarding the mechanisms mediating the effects of temperature and mechanical stimulation associated with surrounding tissues informing the conduct of in-depth research.

Medical physiologists are concerned with the fundamentals of life, while acupuncturists are concerned with how to treat disease and maintain health by stimulating the human sensory system. Thus, the 2021 Nobel Prize opens the door to studying the histological basis of acupuncture and moxibustion and provides several hints informing basic research regarding acupuncture and its clinical translations. These questions are as follows. (1) How do acupuncture and medical massage as physical stimuli exerting effects through touch or mechanical signals conduct signaling, treat pain, regulate homeostasis, and promote healing effects? (2) How do acupuncture and moxibustion change the physiological and pathological state of the human body through the temperature sensing system? (3) What is the distribution of tactile, mechanical and temperature receptors in the skin? Is this distribution associated with meridians and acupoints? (4) How are tactile, mechanical, and temperature sensation signals integrated into the central nervous system, and how does the body respond to these signals? (5) How do other systems in the human body (ie, blood circulation, the immune system, the endocrine system) react and integrate tactile, mechanical, or temperature stimulation? (6) How can the clinical efficacy and application of acupuncture and moxibustion therapies be improved according to these newly discovered acupuncture mechanisms?

Professor Li also raised several basic scientific questions about acupuncture science. (1) Does acupuncture work? (2) Why does acupuncture work? (3) Why does the body have a system that can be activated by acupuncture? (4) How did the acupuncture response system come into being and evolve?

In his presentation, he discussed the relationship between human beings and their external environment and proposed a hypothesis regarding the bionic principle of acupuncture (Figure 1)^[27]. Namely, external injuries such as insect bites can destroy the skin barrier and stimulate tissue defense and the healing response. Acupuncture is “prickly but nontoxic” and can provide the maximum effect with minimal harm. He believes that acupuncture is one such bionic therapy, and that the human body needs external stimulation to produce a repair response. He stated that acupuncture is

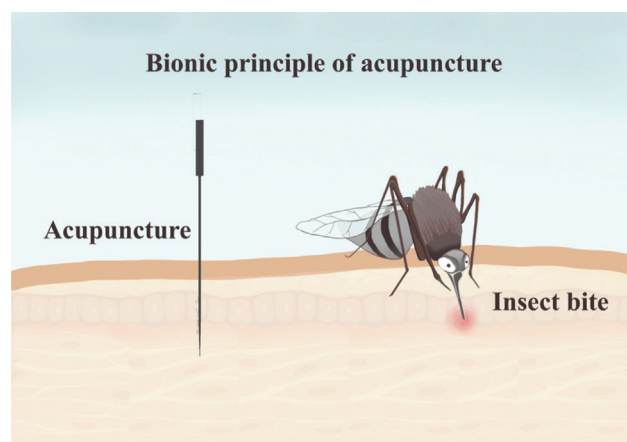


Figure 1. Hypothesis of the bionic principle of acupuncture: external injuries such as insect bites can destroy the skin barrier and stimulate tissue defense and the healing response. Acupuncture is “prickly but nontoxic” and can provide the maximum effect with minimal harm. Image from: Li YM. Finding moving targets for acupuncture: why mast cells? *Zhongguo Zhenjiu* 2021;41(9):965–970.

“prickly but non-toxic” and can achieve a maximum effect with minimal harm.

Based on his previous studies regarding the phenomena of meridians and acupoints as well as the close relationship between mast cells and the effects of acupuncture seen in prior research, Professor Li proposed that these Nobel Prize achievements will promote or have already promoted the study of acupuncture mechanisms. For example, it has been found that mast cells in the skin and in nerve tissue have multiple mechanical receptors on their surfaces that can trigger degranulation *via* mechanical or thermal stimulation, triggering a series of subsequent immune responses. Mast cells are considered moving targets within acupuncture and moxibustion and have been proven to produce specific responses to acupuncture and moxibustion. Mast cells present with special aggregation phenomena at the acupoints and sensitized points of the human body. Their skin distribution density is highly correlated with traditional acupoints and the microneedle system^[28]. He believes that elucidating the relevant molecular mechanisms mediating acupuncture from a mechanical and thermal stimulation aspect will promote our in-depth understanding of acupoints and meridians as well as the mechanisms mediating acupuncture and moxibustion, and will validate and promote the clinical efficacy of these therapies.

Acupoint initiation mechanisms in acupuncture

Professor Yi Guo, Dean of the School of Traditional Chinese Medicine at Tianjin University of Traditional Chinese Medicine, a Tianjin Outstanding Talent, and the Chairman of the Evaluation and Promotion Committee for Suitable Technology in Traditional Chinese Medicine at the World Federation of Chinese Medicine Societies, has been engaged in researching acupuncture mechanisms for more than 30 years. His work has led to influential achievements regarding the mechanisms of acupuncture action, the standardization of traditional Chinese acupuncture, and moxibustion.

In his report entitled “Inspiration from the 2021 Nobel Prize in Physiology or Medicine for Acupuncture Mechanism Research”, Professor Yi Guo first summarized the developmental status of acupuncture clinical practice. Acupuncture is widely used in 183 countries and regions, and a number of high-quality clinical randomized controlled trials (RCTs) conducted in recent years have shown that acupuncture treats functional constipation^[29], stabilizes angina pectoris^[30], and treats stress associated urinary incontinence^[31]. Acupuncture therapy has been recommended within 53 clinical practice guidelines in the United States and within 32 clinical practice guidelines in the United Kingdom. Although evidence to date shows that acupuncture is effective in treating disease, there are several challenges in the further development of acupuncture^[32].

More specifically, the mechanisms mediating the effects of acupuncture are complex. Acupuncture processes can be divided into three components: acupoint stimulation *via* acupuncture, triggering the body’s regulation of the neuroendocrine immune (NEI) network, and producing effects in target organs^[33]. He summarized studies on acupuncture mechanisms published in the last decade, and stated that the research on local acupoints comprises only approximately 2.4% of total acupuncture research.

Therefore, studies on the initiating mechanisms with respect to acupuncture action at local acupoints are few and are neither systematic nor in-depth. Thus, the study of local acupoints is of immense significance and value.

First, local acupoints are the initial response regions with respect to acupuncture stimulation and are also the primary source of the acupuncture effect. To improve the clinical efficacy of acupuncture, we should start with acupoints (ie, the trigger points of the acupuncture effect). Second, the mechanisms mediating the acupuncture effect are complex processes involving the NEI network. In-depth study of initiation mechanisms within acupoints and the general field of acupuncture is likely to determine new modalities for surface stimulus (ie, dry needle therapy). For instance, the Stimulating Peripheral Activity to Relieve Conditions (SPARC) program in the United States is an “acupuncture-like” treatment inspired by acupuncture therapy. Finally, he stated that the mobilization of the body’s self-regulation and protection potential is a guarantor of human health and the key to the treatment of many diseases. The acupuncture principle of “small stimulation, big response” demonstrates that the law of acupoint stimulation in mobilizing the body’s self-regulation and protection potential has important enlightenment value for medical and life science research.

Professor Guo and his research group have been researching on acupoint initiation of acupuncture effects for more than 30 years and have made innovative progress in revealing the initial dynamic mechanisms mediating acupoint stimulation *via* acupuncture (Figure 2).

In terms of the development and application of needle-type biochemical sensors, a variety of needle-type biochemical sensors have been successfully developed. These sensors can carry out *in vivo*, real-time, dynamic, and continuous monitoring of chemical substances associated with deep tissue in acupoint procedures and can realize the simultaneous combination of the acupoint response and the acupuncture effect, thereby providing more effective research techniques and methodology for acupuncture research^[34]. In terms of chemical initiation, this group confirmed the inflammatory reaction in acupoint-based acupuncture, clarified the changes in neurons, mast cells, chemical substances, and blood flow in acupoints occurring in response to acupuncture and their relationships with acupuncture effects, and confirmed the role of mast cells, substance P, and Ca^{2+} in effective acupuncture processes and with respect to the afferent nerve^[35]. A systematic study on acupoint initiation factors showed that acupuncture excites nerve endings at acupoints, and likewise demonstrated a coupling correlation between acupuncture manipulation, coding characteristics of nerve discharge, and acupuncture effects. In terms of establishing the timing network of acupoint affect initiation, this research group first applied a weighted complex network model and analyzed to build a dynamic NEI cell communication network in consideration of the signaling molecules associated with this network to depict the temporal response characteristics of the acupoint network, and to reveal the key factors mediating this response^[36].

Finally, Professor Guo introduced the study of relationships between acupuncture and non-classical ion channels and proposed the hypothesis that acupuncture (namely, physical and mechanical stimulation) may activate the

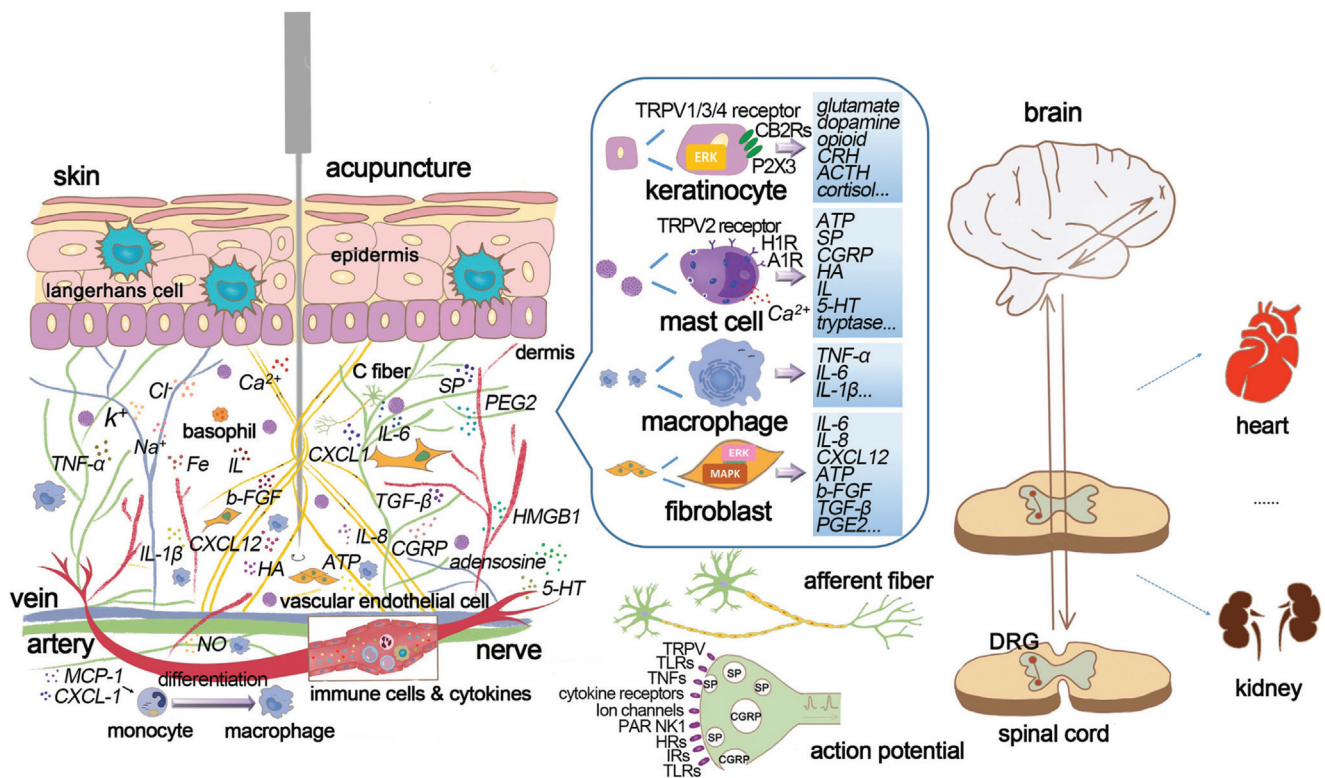


Figure 2. The neuro-immune microenvironment of acupoints-initiation of acupuncture effectiveness Image from: Gong YN, Li NC, Lyu ZX, et al. The neuro-immune microenvironment of acupoints-initiation of acupuncture effectiveness. *J Leukoc Biol* 2020;108(1):189–198.

physical-chemical coupling network through ion channel receptors at acupoints to exert an acupuncture effect. Lifting, twisting, and other acupuncture manipulations produce different forms of mechanical force stimulation and cause physical changes at the acupoint, such that patients experience *deqi* feelings of sour taste, numbness, heaviness, and distention. At the same time, a TCM doctor can feel and produce sinking feelings (for example, a fish swallowing bait), which is a key factor in achieving a curative effect. Acupuncture can also cause moderate tissue damage in the acupoint area, can cause a local benign (orderly and controllable) inflammatory response, can initiate a series of chemical information changes at acupoints, and can cause subsequent biological effects through cascade amplification. However, the mechanisms through which the mechanical force induced by acupuncture is perceived at acupoints are currently unclear. Do local mechanically sensitive ion channels mediate acupuncture effects? How can physical information in acupuncture be transformed into chemical information? Is there a coupling between physical and chemical information in acupuncture?

The ongoing national Natural Science Foundation of China (NSFC) has sponsored a key project entitled “Study on the Initial Mechanisms of Acupuncture Action via a Physicochemical Coupling Network in the Acupoint Microenvironment”. This project, conducted by Professor Guo’s team, aims to solve the above key scientific questions. Professor Guo reported on the preliminary results of this project, showing that acupuncture can activate the TRP, ASIC, and Piezo families within local acupoints. This information will aid in the comprehensive study of biological mechanisms specific to acupoint-based ion channels in mediating the initiation of the acupuncture effect in the near future.

Discussion

Skin distribution of mechanical and temperature receptors

Acupoints are the initial response sites for acupuncture stimulation and the source of the acupuncture effect. More specifically, acupoints are three-dimensional structures composed of a variety of tissues, including skin, subcutaneous tissue, nerves, blood vessels, lymph, tendons, fascia, and muscles. Studies have found a large number of mechanically sensitive ion channels and temperature receptors, including TRPV1, TRPV4 and ASIC3, in nerve terminal and non-nerve cells (ie, skeletal muscle cells and fibroblasts) at different anatomical layers of the local Zusanli (ST36) acupoint. These receptors are denser at the evaluated acupoints than in para-acupoint tissues^[29]. The differences in the distributions of mechanosensory and temperature receptors in skin and muscle when comparing acupoint and para-acupoint regions and the questions of acupoint and meridian specificity are currently unknown. These questions deserve comprehensive study.

Physical stimuli in activating mechanical and thermal receptors in acupoint

Acupuncture, especially traditional acupuncture manipulation, produces different forms of mechanical force stimulation (ie, pressure, tension, shear force) and these single mechanical forms of complex force cause local tissue deformation and displacement, connective tissue contraction, winding needle body, muscle layer pull, and muscle contraction. However, the mechanisms through which the mechanical force derived from acupuncture is transmitted are currently unknown. How does the

mechanical force of acupuncture trigger nerve impulses so that patients can feel *deqi* caused by acupuncture (ie, numbness and sink stretch)? How are the physical signals of acupuncture converted into electrochemical signals? Are physical stimuli (ie, the heat sensation produced by moxibustion and the tactile sensation produced by massage) also transmitted as signals through the sensation system? At present, there is no clear scientific explanation for the above problems, and little is known about the biological principles explaining how acupuncture initiates changes in the acupoint microenvironment. It is known that mechanically-sensitive ion channels can sense mechanical force changes in cell membranes and convert these mechanical signals into electrical or chemical signals, thus playing an important role in various mechanical conduction processes. Several studies have reported preliminary results suggesting that acupuncture at the ST36 acupoint activates TRPV1 receptors expressed on nerve endings and immune cells, promotes ATP release through calcium wave propagation in adjacent nerve endings, and directly acts on nerves to transmit acupuncture information. ST36 injection of capsaicin (a TRPV1 agonist) can reproduce the analgesic effects of acupuncture^[29]. The TRPV2 channel on mast cells in acupoints has likewise been found to participate in the generation of acupuncture effects. TRPV2 channels on mast cell membranes are activated due to the effect of the high stress of acupuncture stimulation, thereby inducing mast cell activation and degranulation, releasing histamine into surrounding tissues, and ultimately resulting in increased concentrations of histamine and adenosine in local tissues. However, after TRPV2 gene knockout, it has been reported that acupuncture induces a lesser degree of mast cell activation and degranulation as well as a weakened acupuncture effect^[30]. Therefore, whether the physical stimulation of acupuncture activates the mechanically-sensitive ion channels on cell membranes and/or promotes the release of chemical molecules that activate nerve endings (*via* cell expression of the ion channel) to initiate the acupuncture effect is a scientific issue worthy of comprehensive study.

Mechanical, tactile, and temperature perception in regulating homeostasis

As previously discussed, mobilizing the body's self-regulation and protection potential is a guarantor of human health and the key to the treatment of many diseases. Acupuncture's "small stimulation, big response" principle can mobilize the body's self-regulation and protection potential and play a critical role in disease prevention and treatment. However, the mechanisms through which mechanical stimulation, tactile and temperature sensing, and various signals within acupuncture and moxibustion cause reactions and integrate into the central nervous system, blood circulation, immune system, endocrine system, and other important human systems are currently unclear. Does differential acupuncture manipulation and intensity activate different ion channels and neural circuits? The latest research conducted by Professor Qiufu Ma demonstrated that the ST36 acupoint expresses PROKR2 positive sensory endings in the deep fascia and the periosteum that drive the vagus-adrenal anti-inflammatory pathway, thus providing a neuroanatomical basis for the selectivity

and specificity of acupoints in driving specific autonomic pathways^[14]. This work has great guiding significance for future research and likewise provides preliminary answers in terms of elucidating acupuncture neural circuits. The nature of acupuncture stimulation itself, including receptors of primary response and the corresponding neural circuits, are of critical and urgent importance within basic, translational, and clinical acupuncture research.

Conclusion

Acupuncture and moxibustion have been found to be effective in most indications on a global scale. These modalities are within the field of physiotherapy, and working through different acupoints and physical factors (ie, mechanical forces or temperature). Therefore, how different physical stimuli derived from acupuncture and moxibustion act on the body and how to comprehensively characterize and apply these effects are key scientific questions to be solved. The winners of the 2021 Nobel Prize in Physiology or Medicine conducted research explaining how the human body perceives mechanical force and temperature, providing an excellent and critical reference for the study of the mechanisms mediating acupuncture efficacy and moxibustion actions. It is important to clarify the molecular mechanisms of the body's perception of acupuncture and moxibustion stimulation as mediated by Piezo, TRP, and other non-classical typical ion channels, and to investigate the mechanistic diversity of different stimulation parameters as well as the specificity of acupoints. These are areas of high research and clinical priority. Moreover, the research ideas and technologies promoted by the winners of the 2021 Nobel Prize have important reference significance with respect to how acupuncture and moxibustion therapy conducts information through acupoints. Cutting-edge neuroscience technologies (eg, electrophysiology, transgenic models, optogenetics) can be used to explain the neural circuits specific to different acupuncture therapies. Finally, using disease models to mimic acupuncture and moxibustion indications, the reviewed research systematically revealed how acupuncture and moxibustion therapies regulate homeostasis from the perspective of acupoint perception, neural circuits, and neuro-endocrine-immune effects in target organs. These efforts help pave the way for exploring ways to improve the clinical efficacy of acupoint stimulation (ie, acupuncture and moxibustion). There is still much work to be done in comprehensively understanding the mechanisms of acupuncture and moxibustion as mediated by ion channel receptors. This research should be carried out in the spirit of the Nobel Prize winners.

Conflict of interest statement

Yi Guo is the editorial board member of this journal. None of the other authors declare any conflicts of interest.

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Ethical approval of studies and informed consent

Not applicable.

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