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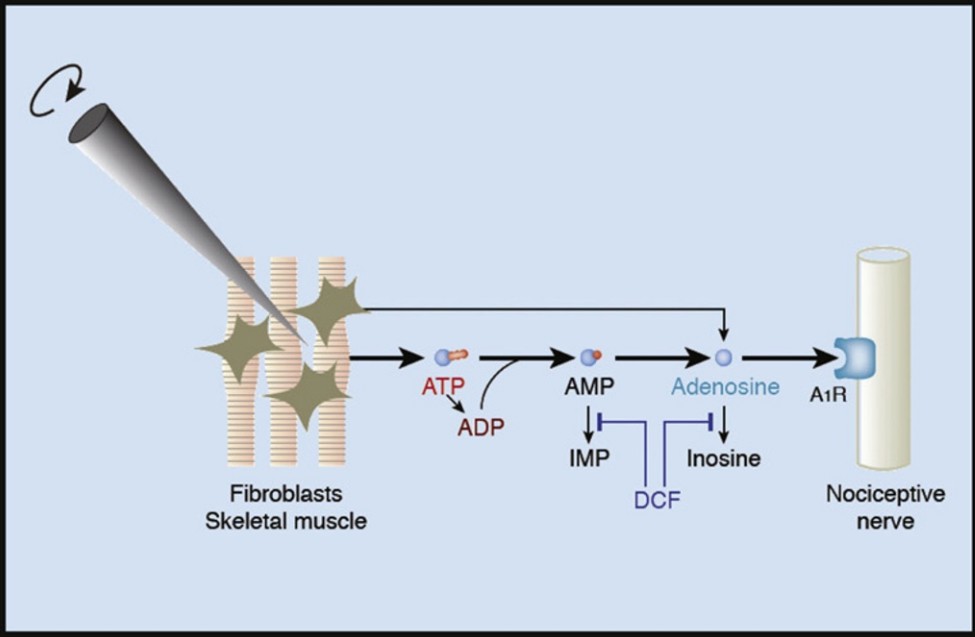

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CHAPTER ONE

History of Acupuncture Research

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Contents

Abstract

The acupuncture has been practiced in China for more than 3000 years and was spread to Europe and American from the sixteenth to the nineteenth century. The history of acupuncture research was initiated in the eighteenth century and developed rapidly since then. In the past, physicians tried hard to apply acupuncture into clinical practice, while scientists were focused on the possible characteristics of acupoints and meridians. In the modern time, scientists have strived hard to evaluate the real effectiveness of acupuncture and the underlying physiological and biological mechanisms of acupuncture. Reviewing research history from past to present, we are delighted to witness this wonderful development. Accumulated evidences that acupuncture is beneficial in various conditions significantly enhanced our understanding the mechanisms of acupuncture treatment. However, there is still no conclusive evidence in acupuncture clinical studies. The clinical research still needs great improving, while the basic research results need to be appropriately transformed into clinical outcomes. Based on current achievements, we believe that although the challenges and difficulties exist, a more

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collaborative, innovative, and integrated approach will help us to achieve further progress in future acupuncture research.

1. INTRODUCTION

Acupuncture has been practiced in China for more than 3000 years and is a natural healing therapy, which has gained increasing popularity and acceptance between public and heathcare professionals worldwide. It was introduced to Korea and Japan in the sixth century AD and spread to the Europe and North America in the sixteenth to nineteenth century AD. In 1971, a report by James Reston in the New York Times about his experience of acupuncture treatment in China exposed countless American for the first time to acupuncture. Since then, acupuncture research has been extensively conducted worldwide. In this chapter, we retrospect the past acupuncture research, review the current achievement, and discuss the challenges faced by acupuncture research in the future.

2. ACUPUNCTURE RESEARCH IN THE PAST

Acupuncture research in the past began in the 1800s and peaked in 1987, when the World Federation of Acupuncture and Moxibustion was formally founded. It comprised of two aspects: clinical and basic research. The studies in this period mainly focused on the pain-related disorders and the nature of acupoint and meridians, providing a solid underpinning for the development and promotion of acupuncture.

2.1. Clinical research

The first literature introducing acupuncture to Europe was published in 1683, by a Dutch doctor Wilhelm Ten Rhijne, who observed the practice of therapeutic needling used in patients with arthritis when he visited Japan (Berman et al., 2004; Bivins, 2001). Then, a German physician Englebert Kaempfer described the acupoints and equipments associated with the acupuncture needles, medical cases, needle holders, and assisted hammers in his book "History of Japan" in 1728 following his tour of Southeast Asia and Japan in the late sixteenth century (Bivins, 2001). However, it took almost 100 years to persuade the European physician to accept the clinical application of acupuncture. The first physician who applied acupuncture into

clinical practice was Dr. Louis Joseph Berlioz in France. He published his case reports in 1816, which contained acupuncture therapy for rheumatism, arthritis, and stiff muscles and joints. The first English monograph on "acupuncturation," as it was generally called at that time, was written by a young surgeon named James Morss Churchill in 1823. He advised needle insertion on the site of pain in the myofascial disorders (Campbell, 2002). At the same time, a number of articles appeared in the scientific literatures such as a Lancet editorial article entitled "Acupuncturation" in 1823 (White, 2004). In 1825, an American, Benjamin Bache Franklin, firstly tested acupuncture analgesia on the prisoners in 1825 (Cassedy, 1974). The following year, he published the first clinical study of the acupuncture modality, a report of his observations on acupuncture for lumbago (low back pain), which may be the first article of acupuncture in the United States (Meng, Xu, & Lao, 2011). Probably the first published British case series, presenting the success of acupuncture in 1000 patients with severe sciatica, was in 1893 (Ernst, 2001).

The development of acupuncture has progressed unceasingly in the time of the twentieth century. The Frenchmen George Soulie de Morant (1878–1955), who was convinced of the importance of acupuncture when he witnessed the effect of acupuncture treatment during an epidemic of cholera in Beijing, got in touch with acupuncture therapy and learned by heart. He published many articles and works on acupuncture and his book "l'Acuponcture chinoise," which systematically introduced the acupoints and meridians, is still regarded as a classic work on acupuncture (De Morant, 1994). Another contributor was Roger de la Fuye, a student of de Morant, who combined the trigger points with acupuncture and drug injection, which greatly improved the clinical effect. Further, he wrote many textbooks on acupuncture and homeopathy (Stollberg, 2006). Due to the increasing interest in acupuncture, the French Acupuncture and Moxibustion Society was established in Paris in the 1940s, the first academic association of acupuncture and moxibustion in the world. In addition, the French physician P. Nogier firstly published the diagram of auricular points in 1957, which described auricular acupuncture treatments for a wide variety of illnesses (Ceniceros & Brown, 1998). These works contributed to spreading acupuncture therapy worldwide.

The acupuncture researches in the past were mostly clinical observation, individual case report, and personal experience introduction, not the systematic clinical trials. In the 1960s, the conception of biostatistics and methodologies, such as randomization that are essential to controlled clinical trials

in Western medicine, has been widely accepted by acupuncture researchers in Asian countries. In the same period, the first controlled clinical trial was conducted in Japan (Shichido, 1996).

In the 1970s, the acupuncture research has step into a modern time. It was all enlightened by the famous report from James Reston in the New York Times in 1971 (Reston, 1971), which described his personal experience that the acupuncture therapy alleviated his abdominal distension after surgery. One year later, US President Richard Nixon visited China and watched the acupuncture performance. The *Journal of the American Medical Association* (JAMA) has firstly reported two articles in 1971, which separately introduced the medical care in China (Dimond, 1971a) and acupuncture anesthesia (Dimond, 1971b). Then, more scientists and medical doctors paid great attentions on the acupuncture phenomena and discussed its real clinical effectiveness.

In 1972, the National Institutes of Health (NIH) in the United States gave its first grant to acupuncture research (Ulett, Han, & Han, 1998). In 1973, the Food and Drug Administration (FDA) in United States has labeled acupuncture needles as "investigational" medical devices (Lytle, 1996). Simultaneously, some researchers discussed about the possibility of double-blind method and efficacy in acupuncture research (Chein & Shapito, 1973; Mark, 1973).

The first influential randomized controlled trial (RCT) on acupuncture was published in NEJM in 1975. Gaw et al. randomly assigned 40 patients with osteoarthritis pain into experimental or control group to assess the pain reduction by acupuncture. However, both experimental and control groups showed a reduction in pain after the treatments (Gaw, Chang, & Shaw, 1975). Another study was conducted to evaluate the chronic shoulder pain relief by acupuncture in 1976. The result showed no statistically significant differences between the classic and placebo acupuncture (the needles did not penetrate the skin) (MOORE & BERK, 1976). Then, Cahn, Carayon, Hill, and Flamant (1978) evaluated the analgesic effect of acupuncture by a double-blind controlled trial in 90 patients undergoing gastroscopy, which revealed real acupuncture could perform easier and better tolerance in endoscopy than control group. In the 1980s, acupuncture research expanded from pain-related conditions to other medical disorders. Pui Fung, Kit Wun Chow, and Yeung So (1986) showed verum significantly reduced the exercise-induced asthma compared to sham acupuncture (SA). At the same time, Jobst et al. (1986) applied acupuncture into patients with chronic obstructive pulmonary disease. Three-week experiment

indicated the traditional acupuncture is more beneficial than placebo acupuncture in terms of subjective scores of breathlessness and six-minute walking distance; however, objective measures of lung function were unchanged in either group.

Take together, acupuncture has been gradually accepted by Western societies. In 1979, FDA classified acupuncture needles as class III (investigational) medical device but allows their clinical use by licensed practitioners (Hammerschlag, 2000). At the same year, WHO listed 43 kinds of diseases and conditions that can be cured by acupuncture and moxibustion, such as nausea and vomiting, pain, addictive diseases, asthma and bronchitis, and rehabilitation of stroke. The acupuncture research has stepped into a new era.

2.2. Basic research

The acupuncture basic research was also originated in the eighteenth century and has gathered increasing interest and acceptance worldwide. In 1755, the Vienna physician Gerard van Swieten wrote down his observation on the physiological communication involved in alleviation of pain using acupuncture and moxibustion (Bo-Ying & Grant, 2001). After that, Roughment combined physiological knowledge with acupuncture and deduced that acupuncture was a kind of counterirritation therapy in 1798 (Birch & Lewith, 2007). This proposal may roughly sketch the model of mechanism underlying acupuncture analgesia. Another important innovation during this time was the electrical stimulation employed in acupuncture basic research. Sarlandiere employed electrical stimulation to the inserted needles to see the altered treatment effects in 1825 (Lu & Needham, 1980). Moreover, other physicians, such as Trousseau, Pidoux, and Duchenne, reintroduced the electrical stimulation into the treatment of chronic pain (Willer, Roby, & Le Bars, 1984).

The acupuncture studies in Japan were initiated during the Meiji Restoration in the latter part of the nineteenth century, which were conducted in a way different from the Western countries. The Japanese scientists and doctors tried to analyze the meridians, acupoints, and potential mechanism by Western-style medical theory. Ohkubo Tekisai in 1894 held a view that acupuncture was a kind of stimulation on the nervous system. Therefore, his style of acupuncture was puncturing on the sympathetic ganglion (Lu & Needham, 1980). On the other hand, Hidetsurumaru et al. were concentrated on the influence of acupuncture and moxibustion on the autonomic

nerve and blood (Chen, 2006). The phenomenon of propagated sensations along meridians was first observed by Japanese physician Yoshio Nagahama in 1946 (Zhu, 1998). Later, Yoshio Nakatani used an electrodermal measurement technology to discover that there were many galvanic points scattered on the skin in 1950. Similar to the classic acupoints, these galvanic points could be matched into lines, named Ryodoraku, which could not only reflect and diagnose the diseases but also balance the body's disorders through some appropriate points (Zhu, 1998). Till now, many Japanese acupuncturists still believe in the correlation between Ryodoraku and the state of autonomic nervous system.

Korean physicians held a totally different view on meridians and acupoints. In the early 1960s, Kim Bongham claimed that he had found the anatomical and physiological basis of meridians, which caught quite a stir over the world. In his studies, he stained out some special ducts and nodes in the subcutaneous tissue, organ surface, and nerve tissues, entitled as Bongham ducts and Bongham corpuscle (Soh, 2012a). However, due to lack of details in the methodology and nonreproducible results, his studies were ignored for almost 40 years. Recently, Korean scientist Soh Kwangsup began to continue Kim's theory and renamed as primo-vascular system to the further acupuncture investigation (Soh, 2012b).

Other scientists utilized modern techniques to analyze the characteristics of meridians and acupoints. In 1961, the French physician Niboyet found that the acupoints have a lower electrical resistance than the surrounding skin (Zhu, 1981). Furthermore, Voll investigated the electrodermal properties of the meridians and acupoints, known as "Electro-acupuncture according to Voll" or EAV and found that almost two-thirds of the EVA points were classic acupoints (Voll, 1975, 1980). These studies significantly enhanced our understanding of biophysical characteristics of the meridians and acupoints.

One important acupuncture research that occurred during the 1970–1980s was the findings of biological and physiological mechanism of acupuncture analgesia. In 1965, the physiologist Melzack and Wall proposed the "gate control theory," which was believed to be related with the plausible mechanism of acupuncture anesthesia (Man & Chen, 1972). Inspired by this theory, Chinese scholar, Professor Zhang Xiangtong, explained acupuncture analgesia mechanism by electrophysiology (Chang, 1978). He suggested that acupuncture analgesia was a result of acupoint afferent impulses and painful areas afferent impulses interacting in the brain. This hypothesis has greatly motivated the other scientists pursuing the

acupuncture research in this direction. In 1972, Professor Han Jisheng and his colleagues collected the cerebrospinal fluid from rabbits that received acupuncture stimulation and infused into others, providing the first evidence that acupuncture alleviates pain by releasing neuromodulatory substances in the brain (Wang, Kain, & White, 2008). A few years later, the scientists have discovered two polypeptides released from the brain with potent opiate agonist activity, called endogenous morphine-like factor or endogenous opiate-like substance (Hughes et al., 1975; Terenius & Wahlström, 1975). Subsequently, Mayer, Price, and Rafii (1977) demonstrated that the naloxone, an antagonist of opiate, could block the acupuncture antinociceptive effect. Furthermore, it has been reported that that opiate receptor knockout CXBK mice had poor electroacupuncture (EA) analgesia effect (Peets & Pomeranz, 1978), suggesting that the endogenous opioids play an important role in acupuncture analgesia. Other researches indicated the involvement of nonopiate mechanisms in acupuncture analgesia as well. A report published in the journal Science in 1982 demonstrated both neural and hormonal pathways and both opiate and nonopiate substances play important roles in the complex modulation of pain transmission (Watkins & Mayer, 1982). In addition, scientists also observed acupuncture tolerance similar to morphine tolerance (Han, Tang, Huang, Liang, & Zhang, 1979). This phenomenon may attribute to the antiopiate substances accompanied with the generation of endogenous opiate substances during the acupuncture stimulation. Later, both Faris, Komisaruk, Watkins, and Mayer (1983) and Han, Ding, and Fan (1985) reported the cholecystokinin octapeptide (CCK-8) had the antagonism function to acupuncture and morphine analgesia, which results in tolerance in the rats (Faris et al., 1983; Han et al., 1985).

3. CURRENT RESEARCH IN ACUPUNCTURE

Since the establishment of the World Federation of Acupuncture and Moxibustion in 1987, the acupuncture research has stepped into a blossom era. In 1995, the Western Pacific Region of the World Health Organization (WHO) announced Acupuncture Clinical Research Specification. In 1996, the US FDA has redefined the conception of acupuncture and moxibustion and admitted them as therapeutic methods. Another revolutionary issue was the NIH Consensus Development Conference on Acupuncture in 1997, which evaluated available scientific information and efficacy of acupuncture in many disorders. In 2007, WHO drafted evidence-based acupuncture and

moxibustion clinical practice guideline, which covered five diseases or symptoms, like depression, migraine, Bell's palsy, herpes zoster, and dysphagia after stroke. All of these events greatly promoted the development of acupuncture. Moreover, the acupuncture development was greatly enhanced in many countries, for example, the German government has funded many acupuncture researches in recent years.

3.1. Clinical research

The clinical research in the present is much different from before. More organizations and institutions have supported clinical researches with various targets. The clinical trial designation becomes more rigorous. The conception of evidence-based medicine provides a great impact on the designations of clinical trials. Most clinical researches currently are large-scaled RCTs, some providing convincing evidences for acupuncture application. Further, the covered diseases and symptoms are more diverse and multisystem. Since scientists and physicians gradually understand that acupuncture can be utilized to treat various kinds of diseases, the emphasis has been transferred from analgesia-related disorders to other diseases, like cancers, digestive and cardiovascular disorders, obstetrics and gynecology problems and withdrawal symptoms, and neurodegenerative diseases. In this part, we will discuss the clinical trials of some diseases and symptoms.

3.1.1 Acupuncture analgesia

Acupuncture analgesia has been applied in diverse kinds of pain-related disorders, especially in musculoskeletal and connective tissue diseases. Acupuncture is commonly used to treat headache and migraine. Many clinical trials were launched to assess the efficacy of acupuncture. Vickers et al. reported that the acupuncture effect in chronic headache is prolonged and beneficial to patients, deserving being incorporated by National Health Service in the United Kingdom (Vickers, 2004). However, two acupuncture clinical trials in patients with chronic pain sponsored by the German government found that although the number of days with headache was reduced by acupuncture compared to baseline, there was no significant difference between the real acupuncture and placebo acupuncture (Linde et al., 2005; Melchart, 2005). There was no suggestion about the cause of conflict results. Two trials in China on the migraine prophylaxis revealed that acupuncture was more effective than flunarizine in decreasing days of migraine

attacks (Wang et al., 2011) but is only a minor effect when compared with SA (Li et al., 2012). These controversial results led to the doubt of effectiveness of verum acupuncture (VA) treatment (Diener et al., 2006).

The efficacy of acupuncture for lower back pain remains a controversy. Studies of acupuncture analgesia effect showed no difference in patients with lower back pain between VA and sham treatment groups (Brinkhaus et al., 2006; Cherkin, 2009). However, a clinical trial found weak evidence of effect of acupuncture at 12 months but stronger evidence of a small benefit at 24 months in patients with persistent nonspecific low back pain (Thomas, 2006).

Although osteoarthritis has been managed by acupuncture for prolonged time, the efficacy of acupuncture is still unclear. Many clinical trials demonstrated acupuncture plus diclofenac was more effective than placebo acupuncture plus diclofenac for osteoarthritis symptoms such as pain relief and joint function improvement (Berman et al., 2004; Vas, 2004). Compared with minimal acupuncture or no acupuncture, some researchers claimed that acupuncture was more effective in clinical scores but faded over time (Witt et al., 2005). However, others claimed the addition of acupuncture to a course of physiotherapy provided no additional improvement in pain relief, and only small benefits were observed in true acupuncture group and nonpenetrating acupuncture group (Foster et al., 2007; Witt et al., 2006). Studies about the influence of expectations on clinical outcome, pooled from four RCT of acupuncture in patients with pain, found a close link between better improvement and higher outcome expectations (Linde et al., 2007).

3.1.2 Other disorders

Abundant clinical trials investigated acupuncture for cancer treatment-related side effects. Acupuncture was used to treat breast cancer chemotherapy-induced emesis, showing that adjunct EA was more effective than minimal needling or antiemetic pharmacotherapy alone, although the effect had limited duration (Shen et al., 2000). In breast cancer patients with vasomotor symptoms, acupuncture treatment not only showed parallel therapeutic effect to venlafaxine, the chosen drug for the symptoms, but also did not induce adverse side effect and improved the energy in those patients (Walker et al., 2010). Further, acupuncture significantly improved joint pain, stiffness, and fatigue in patients with breast cancer (Crew et al., 2010; Molassiotis et al., 2012). Recent studies showed that

radiation-induced dry mouth in cancer patients, both measured by subjective scores and objective salivary flow rates, could be remarkably improved by acupuncture (Meng et al., 2012). All the results suggested acupuncture could be a safe, effective, and durable therapy for cancer treatment-related side effects.

Acupuncture management for gastroenterological problems has always been a hot spot. Early literature has implied acupuncture could induce more tolerance to gastroscopy in patients than placebo acupuncture (Cahn et al., 1978). This efficacy of acupuncture was verified in another study in 2003 (Fanti et al., 2003). In the 1990s, scientists paid more attention to gastric physiology and pathology. EA was suggested to reduce the severity of symptoms in motion sickness (Hu, Stern, & Koch, 1992). Another study showed acupuncture significantly reduced in gastric acid secretion (Lux et al., 1994). A latest survey showed that EA not only exert analgesic for postoperative ileus after laparoscopic surgery but also reduce the duration and hospital stay compared with SA (Ng et al., 2013).

A clinical trial of cardiovascular conditions showed acupuncture has an additional beneficial effect in patients with severe, intensively treated angina pectoris, including the number of angina attacks per week, the performance before onset of pain during exercises, intensity of pain at maximal workload, ST-segment depressions, and quality of life (Richter, Herlitz, & Hjalmarson, 1991). However, when another clinical trial compared the differences between the individualized acupuncture, standardized acupuncture, and invasive SA for hypertension, the outcomes indicated that active acupuncture (individualized and standardized) provided no greater benefit than invasive SA in reducing systolic or diastolic BP (Macklin et al., 2006). A further randomized trial for lowering BP implied that mean 24 h ambulatory blood pressures could be lowered by traditional acupuncture, but the effect disappeared after cessation of acupuncture treatment (Flachskampf et al., 2007). In summary, more evidence is required to testify the effectiveness of acupuncture in cardiovascular system.

Acupuncture has been used in allergic diseases and symptoms for a long time. Clinical trials in patients with eczema showed that acupuncture is effective in improving type I hypersensitivity itch and is equivalent to oral antihistamine drugs (Pfab et al., 2009, 2012). The latest trial published in 2013 provided scientific evidence that acupuncture could significantly improve the quality of life for the patients with seasonal allergic rhinitis and reduce antihistamine use measures compared with SA and cetirizine alone (Brinkhaus et al., 2013).

3.2. Basic research

3.2.1 The nature of acupoints and meridian

The physiological and biological nature of acupoint and meridian remains elusive for years. The recent studies focusing on the connective tissue reported that loose connective tissue may account for the needle-grasp effect shown at acupoints (Langevin, Churchill, & Cipolla, 2001; Langevin, Churchill, Fox, et al., 2001; Langevin & Yandow, 2002). Furthermore, some clinical studies indicated the mast cells in the connective tissue played an important role in acupuncture analgesia (Zhang et al., 2007). Studies on meridians, using nuclear tracer, demonstrated that migration speed and pattern of a radioactive tracer along pathways matching with meridian in patients had neither a vascular nor a lymphatic origin (Darras, de Vernejoul, & Albarede, 1992). The electrical characteristics of acupoints and meridians suggested that acupoints have local electrical resistance/impedance minima with diameters of approximately 1–4 mm, while the meridians have lower electrical impedance and higher capacitance compared to adjacent controls (Darras et al., 1992). Although primo-vascular system (PVS), originated from Kim Bonghan' study, was regarded as an extension of acupuncture meridians (Soh, 2009), there is no sufficient evidences to support the correlation between PVS and traditional Chinese meridians.

3.2.2 The underlying mechanism of acupuncture effect

The mechanisms of acupuncture stimulation have gained a lot of interest and have been extensively investigated. It was reported that individual differences of acupuncture analgesia are associated with inherited genetic factors and the density of CCK receptors (Chae, Park, Hahm, Yi, & Lee, 2006; Lee et al., 2002; Wan, Wilson, Han, & Mogil, 2001). Other studies explored brain regional activity associated with acupuncture analgesia by means of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) and confirmed many brain structures indeed involved in the modulation of acupuncture analgesia (Fang, Krings, Weidemann, Meister, & Thron, 2004; Hsieh et al., 2001; Hui et al., 2000; Kong et al., 2002). In addition, abundant evidences demonstrated that frequency-dependent EA analgesia is mediated by the different opioid receptor subtypes (Han, 2003; Kim, Min, Na, & Park, 2004; Wang, Zhang, Wang, Cao, & Han, 2005; Zhang et al., 2004). While many studies concentrating on central molecular mechanisms of acupuncture reported

that ERK1/2 signal pathway and the downstream events NF-kB, c-fos, and c-jun play important roles in acupuncture effect (Guo et al., 1996; Park et al., 2002; Song et al., 2006), acupuncture could trigger an increased level of interstitial adenosine at the local acupoint, which reduced severity of chronic pain in mice by activating adenosine A1 receptors, while the adenosine A1 receptor gene knockout mice did not show the same responses (Goldman et al., 2010). The similar results were confirmed in human subjects (Takano et al., 2012). This suggests that acupuncture analgesia could be mediated synergistically through the central agents and local agents.

Studies of effect of acupuncture on cardiovascular system demonstrated that acupuncture could diminish regional myocardial ischemia by reduction in cardiac oxygen demand and decrease pressor response (Li, Pitsillides, Rendig, Pan, & Longhurst, 1998). The further investigations indicated that acupuncture could reduce the heightened sympathetic tone through regulation on group III and IV somatic afferents and endogenous opiate system, which lowered myocardial oxygen demand (Chao et al., 1999; Zhou, Fu, Tjen-A-Looi, Li, & Longhurst, 2005). Meanwhile, other clinical trials implied that acupuncture also mediate specific opioid receptors in the rostral ventrolateral medulla (rVLM) (Li, 2001). Recently, other brain regions have been identified to be related with acupuncture regulation on cardiovascular system, like midbrain vlPAG and arcuate nucleus (Li, Tjen-A-Looi, & Longhurst, 2006; Tjen-A-Looi, Li, & Longhurst, 2006).

A series of studies concerning effect of acupuncture on immune system demonstrated that successive EA stimulation at ST36 could enhance splenic NK cell activity in normal rats and mice through increased releasing of IFN-γ and β-endorphin (Hisamitsu, Kasahara, Umezawa, Ishino, & Hisamitsu, 2002; Sato, Yu, Guo, Kasahara, & Hisamitsu, 1996). Other studies demonstrated EA stimulation significantly reduced the elevated serum levels of IgE by suppressing the increase of Th2 cytokines (Park et al., 2004).

Endocrine and metabolic disorders, including obesity and ovulatory dysfunction, have been treated with acupuncture. Recent studies showed that acupuncture could reduce the high levels of ovarian nerve growth factor (NGF), corticotrophin-releasing factor, and endothelin-1 concentrations—all markers for sympathetic activity—and increase low hypothalamic β-endorphin concentrations and immune function (Stener-Victorin & Lindholm, 2004). Moreover, low-frequency EA modulated the sympathetic activity by expressing mRNA and proteins of α_{1a}-, α_{1b}-, α_{1d}-, and β_2-adrenoceptors and the NGF receptor p75NTR and immunohistochemical

expression of tyrosine hydroxylase (Manni, Lundeberg, Holmang, Aloe, & Stener-Victorin, 2005).

4. UTILIZATION OF MODERN TECHNOLOGY IN ACUPUNCTURE RESEARCH

In the past decade, advanced modern technology has been introduced into the acupuncture research for helping understand the central and peripheral mechanism of acupuncture.

Noninvasive neuroimaging techniques have been extensively used in acupuncture studies in the past decade, showing therapeutic effect of acupuncture could modulate neural activity in many cortical and subcortical (i.e., somatosensory, brainstem, limbic, and cerebellum) brain areas both in healthy subjects and in many conditions. Hui et al., by using the BOLD fMRI, observed a concerted attenuation of signal intensity in the limbic system when subjects experienced deqi sensation, indicating a close link between neural activity and deqi sensation (Hui et al., 2005). Positron emission tomography studies showed VA and SA have dramatically different effects on central the opioid receptor-binding ability. VA caused a long-term increase in μ-opioid receptor (MOR), whereas SA led to a decreased MOR (Harris et al., 2009). Another example of good correlation between acupuncture stimulation and brain function is a report from Napadow et al. (2007a, 2007b). FMRI showed that the patients with carpal tunnel syndrome (CTS) had sensorimotor hyperactivation and an overlapping or blurred representation of adjacent fingers within the primary somatosensory cortex. Acupuncture treatment for 5 weeks significantly improved all symptoms of CTS and reduced hyperactivation and overlapping in the sensorimotor cortex (Napadow et al., 2007a, 2007b). PET-CT, studying the brain responses on acupuncture clinical effect for patients with functional dyspepsia (FD), showed that the potential mechanism of acupuncture treating FD is to modulate the homeostatic afferent processing network, providing support for use of acupuncture in clinical practice (Zeng et al., 2012). In addition to these visualized tools, omics technologies have been employed into acupuncture research, including genomics, proteomics, and metabolomics. cDNA microarray analysis demonstrated that 68 genes, which were differentially expressed more than twofold in a neuropathic pain model, could be restored to normal after EA treatment (Lee et al., 2003). EA treatment could affect 10% of the genes of rhesus monkeys with cerebral ischemia, which were involved in signal transduction, cell-cycle control,

metabolism, the stress response, and DNA repair (Guo et al., 2004). Sung et al. reported 36 different proteins expressed between the EA group and nontreated group rats with neuropathic pain (Sung et al., 2004). The proteins associated with inflammation, enzyme metabolism, and signal transduction were restored to the normal levels in rats with neuropathic pain after EA treatment (Sung et al., 2004). Metabolomics is a new technology for studying networks of metabolites in the body and its interaction with the environment. Nuclear magnetic resonance-based metabonomic technique demonstrated that acupuncture stimulation significantly changes the levels of leucine/isoleucine, lactate and glucose, and lipids towards those of healthy control, although this is only a proof-of-principle study due to the limited number of recruited subjects (Wu et al., 2010).

5. FUTURE OF ACUPUNCTURE RESEARCH

5.1. Challenges facing acupuncture research

Although a lot of progress has been made in acupuncture research during the past few decades, there still remain many challenges in the future of acupuncture development. For example, treatments based on syndrome differentiation and individualized treatment protocol are regarded to be fundamental parts of TCM. On the other hand, blinding and standardized controlling are also technically difficult in acupuncture practice. Moreover, there are various kinds of placebo control groups, like SA, nonacupuncture, and minimal acupuncture, making clinical trial studies more complicated and reducing the efficacy of acupuncture. How to reconcile those factors in the acupuncture research in particular clinical acupuncture studies are the big challenges faced by the acupuncture research community. The need for the unified standard and evaluation indexes particularly in acupuncture clinical study might be one of the rationales.

Although basic research, performed mostly in animal models and health human subjects, reported very encouraging physiological effects of acupuncture, the results from clinical trials are less encouraging or minimal at the best. It is very likely, based on our present knowledge, that the animal models employed for mechanistic studies of acupuncture are not within the explanatory framework of fundamentals of acupuncture treatment such as "qi," meridians, and acupoints and there is an urgent need to develop better animal models in which all those essential parts can be illustrated.

5.2. Directions of future acupuncture research

There is mounting evidence proving acupuncture treatment is superior to usual care. However, acupuncture treatment is, at most, only marginally more effective than SA, which, when compared to no treatment, is associated with larger effect sizes than when conventional placebos are compared to no treatment. These lead to a hypothesis that acupuncture may be a placebo intervention, which is just needling into the skin at any positions of the body. However, the truth is that acupuncture is a complex intervention with placebo effect, nonspecific physiological effects to needle insertion, and specific effect. The future acupuncture research not only needs to emphasize acupoint effective specificity but also needs to identify key physiological and psychological nonneedle components of acupuncture treatment to minimize specific nonneedle effects in sham treatment.

The translational medicine in acupuncture research means the future researches need to make a bridge connecting the laboratory mechanism with the clinical outcomes. The various needling parameters, such as depth, frequency, angle, and twirling, have a great impact on the acupuncture effect. The acupuncture also could influence numerous biomarkers testified in the laboratory. Together, all these could improve the correlations between the needling parameters, biomarker changes, and clinical outcomes.

5.3. Methodology, design, and evaluation of clinical studies

The high-quality RCTs indicate that large-scale, well-designed trials such as real randomization, rational controlling, and rigorous blinding are necessary in the future of acupuncture clinical studies. The real randomization includes two aspects: a method of getting randomly assigned sequence and hiding procedure during the implementation allocation. It could prevent psychological bias from the acupuncturists and patients. Rational controlling is one of the important methods to remove the placebo effect of acupuncture. The most controlled methods in China are different acupuncture techniques, like placebo needle, nonspecific acupoint, SA, and minimal acupuncture. The clinical researches in the future need more scientifically advanced controlled methods, providing a more objective evaluation of acupuncture effect. It is also very important to perform blinding control in acupuncture practice. Most trials about acupuncture are single-blind, while the double-blind mentioned usually refer to the subjects and evaluators being blinded instead of acupuncturists. Even though, rigorous and explicit blinding remains necessary in the practice.

Referred to the clinical outcome evaluation, the research in the future should focus on the more objective and reliable measurements, like symptom and function scales and life quality evaluation. Some biomarkers tested from the laboratory could also be brought into TCM outcome criteria, which could better reflect the acupuncture effect. Furthermore, the evaluation in the future should put more emphasis on the efficacy, effectiveness, and cost-effectiveness. The effectiveness is comparing to the waiting list control, while the efficacy is comparing to the nonpenetrating and penetrating SA. The cost-effectiveness in the healthcare insurance should also be seriously considered in order to offer a sustainable and affordable approach to millions of peoples with different conditions.

6. SUMMARY

Acupuncture research has a very long history. It initiated in the eighteenth century and grew rapidly up to now. Scientists and clinicians have strived hard to understand the physiological and biological mechanism of acupuncture effect and evaluate the real effectiveness of acupuncture in clinical practice. Reviewing research history from past to present, we are delighted to witness this rapid and wonderful development. So far, cumulative evidences demonstrated that acupuncture is beneficial in various conditions. Moreover, the underlying mechanism can partly be interpreted by modern advanced science and technology. However, there is still a shortage of conclusive evidence in clinical trials. Further, there are many very important issues surrounding acupuncture research, such as underlying mechanisms of acupuncture needling, acupoint specificity, and understanding how individual factors of acupuncture treatment interact and translate into physiological and clinical outcome, that need to be solved before maximizing clinical beneficial of acupuncture treatment.

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