

Review Article

Acupuncture research in Taiwan

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Abstract

Taiwan has a unique cultural milieu and integrated medical education so that is a bellwether for acupuncture research. Pioneer researches here on electrophysiology and neuroendocrine illustrate a crucial role of the central nervous system (CNS) plays in acupuncture treatment. With different frequency of stimulation, acupuncture can elicit different physiologic responses in the CNS and neuroendocrine systems. Researches in Taiwan on the autonomic nervous system (ANS), cardiovascular system, meridian theory, and acupoint specificity further shed light on the mechanism of acupuncture treatment. The strong research background in Taiwan enables clinicians here to conduct integrated trials on different disorders. Pain syndromes and neurologic disorders are the leading issues on acupuncture clinical trials. Novel concepts and studies hailed from Taiwan have great impact worldwide. In addition to pain syndromes, Taiwanese clinicians pay much attention to diverse kinds of diseases. This broadens the spectrum of acupuncture trials and clinical application of acupuncture treatment. The exploration conducted in Taiwan leads acupuncture research worldwide.

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Introduction

Situated in the West Pacific on the Rim of Fire, Taiwan is a multicultural country that calls itself the sovereign Republic of China (R.O.C.). During the Age of Discovery (1492–1769), Western sailors conducted trade with Taiwan and in 1624 the Dutch East India Company occupied the southern coast of Taiwan and made it a Dutch entrepôt in East Asia. During Dutch occupation, Dutch missionaries preached Christianity to the inhabitants of southern Taiwan. The Dutch developed colonial agriculture in Taiwan. They recruited laborers from Fukien Province to work on the sugar plantations. At the end of the Dutch colonial period, there were about 100,000

Chinese plantation workers on Taiwan. In the 20th century, western missionaries introduced western medicine to Taiwan, and, when World War II ended in 1945, 50 years of effective Japanese rule also ended and Taiwan came under Chinese rule. Modern medical institutes were founded by the R.O.C. government. Thus, Taiwan provides a unique, integrated medical education.

China Medical University (CMU), founded on June 6, 1958, as the China Medical College, became Taiwan's first academic institution providing both Chinese medicine and pharmacy programs to medical students. Graduates from the School of Chinese Medicine in the CMU are proficient in their knowledge of western and Chinese medicines, and the majority achieves joint licensure in Western and Chinese medicine after passing their national exams. This medical program has proven to be a successful means for training doctors of a new generation. In 1996, on the basis of our experience in the CMU, our group was invited to found the

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To improve resources for research into traditional Chinese medicine (TCM), the Graduate Institute of Chinese Medical Science was established in 1975 by the CMU and a doctoral program has been provided since 1988. Since then, increasing numbers of researchers have dedicated themselves to TCM investigations, including herbal medicine, acupuncture, TCM theory, and classic canons, among others. In view of the growing need for integration of both theory and practice between TCM and Western medicine, the Graduate Institute of Integrated Medicine was established in 1998 by the CMU. In 2005, the CMU established the Graduate Institute of Acupuncture Science, the first specialized acupuncture research institute in Taiwan. Many graduate clinicians from both the CMU and Chang Gung University are nowadays concentrating on acupuncture studies and the number of acupuncture research institutes is increasing in Taiwan.

The aim of this paper is two-fold: to introduce some of the most forward-looking and interesting acupuncture research currently being conducted in Taiwan, with an initial focus on the basic investigations into the mechanisms of acupuncture and meridian science research. The paper then highlights data from clinical trial findings.

Basic investigations

It is widely believed that the “De Qi” sensations felt during acupuncture treatments significantly increase their therapeutic effectiveness. De Qi is a painless sensation characterized by numbness, dullness, soreness or heaviness, leading to the hypothesis that the central nervous system (CNS) is responsible for the therapeutic effects of acupuncture. For example, the CNS is where acupuncture analgesic effects occur [1]. Early studies conducted in monkeys have demonstrated an increase in the pain threshold due to acupuncture [2]. According to our studies, acupuncture is able to alter CNS sensory processing. For instance, electrophysiologic studies demonstrate that supraspinal needling at specific acupoints suppresses the sympathetic skin response [3], cutaneous [4], and blink reflexes [5]. These results suggested that acupuncture fails to influence the monosynaptic reflex located in the brainstem and at the spinal level. Indeed, by utilizing auditory endogenous potentials (P300), we have previously found that the cerebral cortex is the major location where acupuncture interferes with sensory processing [6]. Few researchers beside ourselves have explored the effects of acupuncture through electrophysiologic studies. The high level of proficiency in western and Chinese medicines amongst the medical staff in our group gives us the ability to competently research both medicinal doctrines.

In addition to our electrophysiologic studies, many Taiwan researchers have focused on the neuroendocrine effects of acupuncture in the CNS. For example, Cheng and colleagues [7–9] found that scalp acupuncture at the GV20 (Baihui) site can activate central noradrenergic [7] and serotonergic [8] monoamines in rats, which can further reduce memory

storage deficits [9]. Subsequent research suggests that not only scalp, but also somatic, acupuncture can activate central monoamine release (dopamine [10]). Similarly, cholinergic and opioidergic activities in the nucleus tractus solitarius (NTS) have been observed after scalp electroacupuncture (EA). Chang's studies [11,12] have shown that EA at the Annian acupoint (EX17) can alter sleep Electroencephalography (EEG) patterns in rats via cholinergic and opioidergic pathways in the NTS. These effects are point-specific, as needling at nonacupoint sites elicit no such effects in the CNS. These research outcomes provided good scientific evidence for clinical practice and trial investigations, which will be discussed further in this paper.

Researchers in Taiwan have paid much attention to the effects of different EA frequencies. For instance, our electrophysiological studies have revealed that applying varying frequencies of transcutaneous electrical nerve stimulation (TENS) to acupoints results in variable physiological responses [13]. Likewise, Lin and colleagues have shown that different EA frequencies activate different serotonergic pathway. Using different serotonin antagonists to analyze the analgesic effects of EA, these researchers concluded that EA analgesia is mediated by 5-HT_{1a} and 5-HT₃ receptors at both low and high frequencies; however, when applied at a higher frequency (100 Hz), EA can result in additional effects on the 5-HT₂ receptor [14–16]. Recently, exciting data were released by Shen and Lai [10] in their frequency-specific acupuncture study that used frequencies varying between 6 and 30 Hz, interspersed by intervals of 3 Hz. This study found that only 6, 15, and 21 Hz EA frequencies at the PC7 (Daling) site will increase brain dopamine levels, in a time-dependent manner; specifically, stimulation at 6 and 15 Hz induced an immediate response, while 21 Hz induced a response only after stimulation ceased. EA frequency is therefore the major determinant in the therapeutic effectiveness of acupuncture treatments.

Some research groups have attempted to elucidate the role of the autonomic nervous system (ANS) in acupuncture therapy. Disturbances in the ANS have been implicated as being a major contributor to many disease states. For example, Lin and colleagues [17] have focused on the relationship between the ANS and the cardiovascular system (CVS). Their work has suggested that EA at the LI4 (Hegu) site can elicit a pressor effect on blood pressure. Notably, lower (2 or 3 Hz) and higher (20 or 30 Hz) frequencies of EA differentially increase blood pressure via different ANS pathways. Whereas a lower EA frequency increases vascular sympathetic activity and results in a pressor effect displaying a tonic pattern, a higher frequency increases cardiac sympathetic activity exhibiting a phasic pattern [17–20]. This is another example of how EA is associated with frequency-dependent differences.

Moreover, acupuncture is associated with point-specific differences. According to Chang and colleagues [21,22], EA at the BL15 (Xinshu) site, as well as scalp (Sishengcong) and auricular (Shenmen) sites, increased the normalized high frequency power component and decreased the normalized low frequency power part of the heart rate variability (HRV) and

pulse rate variability (PRV), which implies an enhancement of parasympathetic activity by acupuncture. Interestingly, our own studies have suggested that needling at the TE5 (Waiguan) site increases the capillary density of hand nail fold microcirculation through segmental sympathetic inhibition [23], whereas needling at the ST36 (Zusanli) site did not affect hand cutaneous blood flow [24]. Although these conflicting results might be due to the different acupoints chosen, we are contemplating other explanations.

We have shown that bilateral EA at the ST36 acupoint results in both sympathetic and parasympathetic responses (decreasing the heart rate and skin temperature) in healthy volunteers [25]. Furthermore, we found that the physiologic responses to ST36 stimulation differed in the dorsum and palm, which suggests that acupoint stimulation may have different effects in different parts of the one organism. For example, 2 Hz of bilateral EA at the ST36 site decreases the cutaneous temperature in the dorsum of the hand, whereas no change in temperature has been observed in the palm of the hand during EA stimulation [24]. It appears that stimulation at different acupoints causes variable responses in the same bodily organ, while stimulation at the same acupoint can result in variable responses throughout different organs of the body.

Given the intricate theory of TCM and the complicated networks of the CNS, the complex physiological responses to acupuncture are not surprising. Functional magnetic resonance imaging (fMRI) was once regarded as a novel tool to elucidate the CNS effect of acupuncture. Indeed, Ho and colleagues [26,27] have suggested that certain brain regions are activated, with point-specific properties, in experimental animals. In human participants, needling at traditional analgesic points (ST36 and LI4) can enhance signals from the analgesic matrix (hypothalamus and nucleus accumbens) and reduce signals from the pain perception area (limbic system) [28]. However, some data are impossible to replicate due to the sophisticated level of data processing needed and analysis required for the blood oxygenation-level dependent (BOLD) signals. Lin and colleagues [29] noted that carryover effects of block design (on- and off-treatment) research interfere with results from acupuncture fMRI investigations.

Much evidence shows the effect of acupuncture on the neural and endocrine systems; Wang and colleagues have focused on the cardiovascular system. It has been suggested that acupuncture at any given point belonging to the same meridian should result in similar changes to the pulse spectrum of the radial artery [30–32]. According to the resonance theory, changes in the pulse spectrum reflect the circulatory status of inner organs and elucidate the microcirculatory properties of acupoints [33]. Indeed, compared with non-acupoint sites, acupoints have been shown to possess specific microcirculatory characteristics [34–36] that have specific responses to acupuncture stimulation [37,38]. Therefore, it is speculated that acupuncture at any specific acupoint can regulate the blood supply of its associated inner organ(s). This hypothesis leads us in a new direction into research involving the meridian theory.

Another innovative line of research is exemplified by the diabetic studies of Chang and colleagues [39]. They have found that 15 Hz of EA at the CV12 (Zhongwan) site had hypoglycemic effects in normal rats and a rat model for non-insulin-dependent diabetes mellitus (Type II DM) [39]. This insulin-hypoglycemic effect is mediated by opioid [40,41] and serotonin [15] peptides. Notably, 15 Hz of bilateral EA at the ST36 (Zusanli) site can further improve insulin sensitivity [42] by lowering free fatty acid levels in an insulin-resistance model [43]. Similarly, we have revealed that EA at the ST36 acupoint can modulate blood glucose and increase the metabolic rate at the cellular level [44]. These results imply that acupuncture treatment is clinically feasible in the metabolic syndrome.

Clinical trials

In Taiwan, many hospitals have TCM departments and even Integrated Western and Chinese Medicine departments, enabling clinical trials to be designed and conducted more easily. Most of the clinicians in these departments are officially licensed as both western and Chinese medical doctors, who have acquired a deep knowledge of acupuncture and much clinical experience that can be used in acupuncture trials involving inpatients. Notably, hospitalized patients are more willing to seek and accept acupuncture treatment in those hospitals that provide TCM and Integrated Western and Chinese Medicine departments.

Most worldwide acupuncture clinical trials have assessed pain syndromes (headache, low back pain, and postoperative pain, among others [45]). However, acupuncture has been used within Chinese societies for many diverse diseases besides pain syndromes. Taiwanese clinicians have accordingly researched a wide spectrum of diseases. The CMU, Chang Gung Memorial Hospital, and National Yang-Ming University are the largest TCM research institutes in Taiwan and have conducted the majority of acupuncture trials there to date. Among these, trials from the CMU outnumber all other institutions.

In Taiwan, a popular area of investigation is the effect of acupuncture treatment on various neurologic disorders. Patients with these disorders usually have to undergo long-term rehabilitation to improve their disabled functions. However, Wong and colleagues [46,47] have suggested that electric stimulation at some acupoints may enhance neurologic function in patients with hemiplegic stroke and spinal cord injury. Further randomized controlled trial (RCT) investigations have implied a greater improvement in balance among stroke patients treated by true manual acupuncture [48]. Compared with the control group who received acupuncture treatment without the sensation of De Qi, true manual acupuncture at the GV20 (Baihui) site as well as at four spirit acupoints elicited an immediate effect on several balance parameters. In addition to scalp acupuncture, EA at cognition-related acupoints enhanced the cognitive function in patients with stroke [49]. Lin and colleagues concluded that EA at acupoints PC6 (Neiquan) and HT7 (Shenmen) was a promising complementary therapy for rehabilitation of patients with

stroke. These data [46–49] indicate that acupuncture treatments have beneficial effects on the ischemic brain. Indeed, our previous animal studies have revealed that EA at the ST36 (Zusanli) site increased cerebral blood flow (CBF) in cerebral ischemic rats [50], while acupuncture at the GV20 (Baihui) site enhanced dopamine levels and protected neurons from apoptosis in ischemia-reperfusion injured brains of rats [51].

Many leading trials involving acupuncture for analgesia have been conducted in Taiwan. In the RCT by Lin and colleagues [52], the effectiveness of acupuncture-induced analgesia was assessed for postoperative pain. A total of 100 patients scheduled to have lower abdominal surgeries were included and randomly allocated to one of four treatment regimens: Group I ($n = 25$), control; Group II ($n = 25$), sham-EA (needle insertion without electrical stimulation); Group III ($n = 25$), low-EA (2 Hz of electrical stimulation); and Group IV ($n = 25$), high-EA (100 Hz of electrical stimulation). Postoperative morphine requirement was significantly reduced in patients who received preoperative treatment with both low-EA and high-EA. Subsequent RCTs have also revealed that stimulation at the SP6 (Sanyinjiao) site produces reliable adjuvant analgesia for labor pain [53] and C-section pain [54].

Some chronic pain syndromes are often treated by acupuncture in the clinical setting, as people suffering chronic pain are more willing to seek alternative therapies. This situation is especially so in Taiwan. For example, frozen shoulder and osteoarthritis (OA) of the knee are common degenerative disorders of the joints that cause not only pain but also functional disability. Long-term medication and rehabilitation programs are often associated with side effects and poor compliance. Such patients comprise the majority of those presenting at acupuncture clinics. An RCT has shown that acupuncture treatment had greater pain relieving effects than physical therapy. Combining acupuncture with physical therapies can achieve greater functional improvement of frozen shoulder [55], as is the case for knee OA, whereby EA has significantly improved gait performance and pain severity [56]. Of note, this recently published RCT suggested that gait analysis is a more appropriate means for measuring the efficacy of acupuncture treatment than the visual analogue scale (VAS), the standard tool for rating of pain.

A previous review [45] has suggested that the assessment tool is a vital determinant of studies evaluating the effectiveness of acupuncture analgesia. Importantly, higher cortical modulation of pain perception can be easily influenced by the placebo effect. Clinical trials that use only the VAS as an assessment tool run the risk of allowing the powerful placebo effect of sham acupuncture to mask specific therapeutic effects associated with acupuncture. An objective assessment tool is therefore needed for acupuncture analgesic studies. In our own RCT, we found that acupuncture and steroid injection improved global symptom scores to the same extent in patients with carpal tunnel syndrome [57]. Objective changes in nerve conduction studies (NCS) in the acupuncture group showed significant improvements from baseline and in comparison to steroid treatment. Outcomes from studies that lack an

objective assessment tool such as the NCS will be criticized for the placebo effect.

In addition to neurologic and painful disorders, other chronic disorders, some of which may be difficult to treat with western medicine, have been successfully treated with acupuncture in Taiwan. For example, acupuncture treatment has improved the quality of life [58] and resulted in an immediate bronchodilating effect [59] in patients with asthma. Acupuncture has also been evaluated in allergic rhinitis. In their analysis of gene expression, Chang and colleagues found that acupuncture treatment restored the balance of proinflammatory and anti-inflammatory cytokines in patients with allergic rhinitis [60]. These researchers further suggested that the therapeutic effect of acupuncture differed according to the patients' gene expression profile [61]. This novel finding highlights an important concept of personalized acupuncture treatment. According to TCM theory, different people with different constitutions need different treatment formulae. The concepts of "pattern identification" and "syndrome differentiation and treatment" are keys to the practice of TCM, including acupuncture, concepts that contrast starkly with the standardized formulae used in modern trials. Indeed, a few researchers have proposed that it is necessary to distinguish the disorder in an individual patient by characterizing "pattern identification" before starting the trial. This aspect has been addressed by some recent research, as in explorations by our group, in which we have identified common "patterns" in patients with acute stage cerebral infarction at the CMU hospital [62].

Another example of refractory disorders that has been successfully treated by acupuncture in Taiwan is uremia [end-stage renal disease (ESRD)]. While acupuncture cannot wholly cure uremia, this treatment modality may successfully deal with some uremia-related symptoms. For instance, evidence suggests that acupuncture at the LI11 (Quchi) site is an effective means of relief for uremic pruritus [63]. Although the study authors concluded that acupuncture was a safe procedure for hemodialysis patients, safety concerns remain as to possible side effects of the invasive needling (such as infection and bleeding). Acupoint massage (acupressure) and other noninvasive stimulations at acupoints have therefore been considered as alternatives. Accordingly, acupressure at kidney-related points (i.e., KI1 Yongquan, SP6 sanyinjiao) has demonstrated lower levels of fatigue, improved quality of sleep and less depressed mood compared with patients with ESRD in a control group [64–67]. Other noninvasive (infrared [68] and electrical [66]) stimulations at acupoints have shown similar effects. These noninvasive methods are particularly suitable for provision by nurses, patients and their families.

Obesity and the associated metabolic syndrome have become a major health issue worldwide. In Taiwan, acupuncture is a popular means for weight reduction. Two different methods are used for weight reduction; somatic (body) and auricular (ear) acupuncture. Each offers certain advantages. For example, it is claimed that somatic acupuncture enhances local metabolism, whereas auricular acupuncture is faster and more convenient in the clinical setting.

Crossover and pilot trials performed by Chou and colleagues [69,70] have documented beneficial effects of EA on body weight, body mass index, and waist circumference in obese women. These trials used the somatic acupoints CV6, CV9, ST28, and K14 on the abdomen and ST36, ST40, and SP6 on the legs, as according to TCM theory and expert advice. As regards auricular acupuncture, certain trials have suggested possible mechanisms that could have involved in weight reduction. For instance, our findings have implied the involvement of the ANS (a sympathomimetic effect) [71], while Chang and colleagues [72] have indicated that leptin and ghrelin may play a role.

Conclusion

This paper shows that acupuncture research in Taiwan differs markedly from investigations conducted in Western countries, which have focused on a broader spectrum of disorders and entities.

As highlighted in this paper, the explorations conducted in Taiwan are leading research worldwide. For example, our group is interested in the electrophysiologic effects of acupuncture [3–6,13], while Chang and colleagues [15,39,40,42,43] are investigating its hypoglycemic effect. Wang and colleagues [34–38,73] are exploring the properties of acupoints and the meridian theory. Taiwanese clinical trials of acupuncture involve specialists from almost all disciplines, from neurology [46–49, 57,74], rheumatology [58–60], nephrology [46,63–68], endocrinology [69–72], gastroenterology [75–77], obstetrics [53,54], ophthalmology [78,79] and, of course, pain [52,55, 57,80]. This paper has shown that researchers in Taiwan play a very important role in acupuncture investigations. We are determined to continue to encourage both the quality and quantity of acupuncture research.

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