Chapter 1

Current Trends in Acupuncture Research: From Analgesia to Physiological Function of Brain

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/55184

1. Introduction

Acupuncture has been used for different kinds of disorders for a long period of time in Asian [1] and currently been accepted by western countries by virtue of its obvious efficacy and scientific evidences on basic and clinical studies. As a part of Traditional Chinese Medicine (TCM), acupuncture may be the most evident therapy among all other complementary and alternative medicines (CAMs). This chapter is going to discuss current trends in basic acupuncture research and clinical trials.

Early findings of acupuncture analgesia inspired following studies with the opioid- and serotonin-mediated descending inhibitory pathways [2]. In central nervous system (CNS), acupuncture, especially electroacupuncture (EA), activates many cortical and subcortical regions involved in these pathways. Noteworthy, the EA effects are frequency-dependent. For example, lower frequency EA (1-5Hz) possesses prominent anti-hyperalgesic and anti-inflammatory effects whereas higher (100Hz) one has more effect on cortical serotoninergic system. Accordingly, different frequency EA initiates different pathways. At more peripheral level, the analgesic effects of acupuncture are partly explained by modulation of synaptic plasticity and cholinergic reflex. The relationship between cholinergic reflex and acupuncture has been postulated for decades. Currently, more and more evidences support this assumption [3]. Electrophysiology is a promising tool to investigate neurophysiology. Compelling evidences have clarified the acupuncture effect on electrophysiological profiles. One of the important contributions of electrophysiology is to consolidate the idea that acupuncture act through high cortical conditioning. In addition to traditional histological and electrophysiological studies, advent of neural functional imaging provides more impetus for CNS func-

tioning during acupuncture [4]. Since CNS is the major modulator of homeostasis, acupuncture also effectively to regulate metabolic penal, such as blood glucose and lipid.

In the eras of randomized control trial (RCT), acupuncture need to be verified by more rigid method. In addition to methodological and sham designs, we found that acupoint selection and assessment tool are equally important. Especially in trials for pain syndromes, inadequacy of acupoint or outcome measurement often elicits biased conclusion. The idea is that there are three distinct physiological effects of acupuncture, namely, point-specific effect, placebo and non-specific physiologic effects to needle insertion; some of them overlap with sham and placebo controls which are the methods widely used in current acupuncture RCTs. Several cases in point will be discussed in this chapter.

Among many acupuncture RCTs that have been published in the past decades, pain syndromes are explored most extensively. The present chapter is going to take chronic headache, low back pain, osteoarthritis and postoperative pain as examples. Although most of the data suggested better outcomes after acupuncture treatment, we can still find the fact that not every pain syndrome is suitable for standardized and inflexible acupuncture trials. Another encouraging issue currently is using acupuncture to treat neurological disorder, such as stroke and peripheral neuropathy. Acupuncture now is a rising star for the treatment of stroke. Many pioneer trials have demonstrated the beneficial effect of acupuncture treatment on stroke rehabilitation. Others will also be mentioned here are disorders such as metabolic syndrome and atopic disorders. The nature of uncontrollable inflammation of these lingering disorders makes them the next in the spotlight, since postulated role of acupuncture may regulate inflammation.

From analgesic effect of acupuncture to physiological function of brain, acupuncture researches have made their own mark on scientific world.

2. Mechanism of acupuncture analgesia

2.1. Inspiring findings from the studies of mechanisms of Acupuncture Analgesia (AA)

Analgesic effect is the most studied one among the variety clinical applications of acupuncture. As the scientists all over the world have devoted themselves into this field, several evidences are brought forward [1, 2]. The starting place is gate control theory [5]. It is believed that acupuncture stimulation activates larger Aβ nerve fiber which then "gates" the nociceptive signals from Aδ and C nerve fibers in substantia gelatinosa (SG) in spinal dorsal horn. However, gate control theory can only explain transient and local AA within the same and adjacent dermatomes where painful areas are. Gating control cannot produce distal and prolonged AA. Therefore, widespread regulation elicited by acupuncture at spinal and supraspinal levels has been the central question to be addressed for decades.

http://dx.doi.org/10.5772/55184

To view the whole picture of AA, quick review of central endogenous opioid system and descending inhibitory pathways is necessary. Purification of β-endorphin, enkephalin and dynorphin in late 1970s [6] gave rise to the accelerated progress on the understanding of central endogenous opioid systems, as well as mechanism of AA. The arcuate nucleus in hypothalamus and periaqueduct gray (PAG) in midbrain are the major locations releasing beta-endorphin and enkephalin [7]. Arcuate nucleus projects endorphinergic axons to PAG, and then PAG sends endorphinergic axons to nucleus raphes magnus (NRM). This arcuate-PAG-NRM axis is the center of "descending inhibitory pathway". For example, stimulating PAG with electrical or opioids produces analgesia [7]. NRM has widespread serotoninergic projection to spinal cord, and mainly has synapse with enkephalinergic inhibitory interneurons in SG of spinal dorsal horn. Another counterpart descending inhibitory pathway of arcuate-PAG-NRM axis involves parabranchial nucleus (PBN). Unlike arcuate nucleus, PBN releases dynorphin instead of beta-endorphin or enkephalin to PAG. In both descending pathways, spinal endogenous opioid presynaptically knocks out/down nociceptive signals [8]. The relationship between the abovementioned endogenous opioid system and AA date back to 1970s, illustrated by the finding that Naloxone, an nonselective antagonist to opioid receptors, attenuates analgesic effect of acupuncture in human [9] and mice [10].

Based on progress of the knowledge of different endogenous opioids, compelling evidences have more directly revealed the relationship between AA and endogenous opioids [11-13]. Furthermore, researches also demonstrated the characterized frequency-dependent effect of EA on the release of different endogenous [14]. This early observation inspired later researches on EA. The most well-known ones are conducted by Han's group. The frequency-dependent characteristic of EA hasn't been elucidated until the experiments of his group. They reported that in EA, frequency of electrical stimulation determines the pathway it could activate [15]. For example, by using a cross-tolerance technique, lower frequency (2 Hz) EA produces analgesia through μ- and δ-opioid receptors and that higher frequency (100 Hz) EA through the κ-opioid receptor. They concluded that 2 Hz EA stimulates the release of β-endophin, enkephalin and endomorphin [16, 17] within the network of the CNS and that 100 Hz EA releases dynorphin [18]. Taken together with descending inhibitory pathways, lower frequency (2Hz) EA is postulated to active arcuate-PAG-NRM pathway and higher (100Hz) one to activate PBN-PAG-NRM.

Although we have already known that AA is speculated emanated form endogenous opioids and related descending inhibitory pathways [11, 19], hypothalamus-pituitary axis is still a possible source of endogenous opioids mediated AA [10]. These two mechanisms (hormone and neurotransmitter) are not mutually exclusive because different stimulating protocol, not only frequency but pulse width of EA, can yield different effects [20]. We assume that hormonal mechanism produces its analgesic effect via anti-inflammation in a gradual mode whereas endogenous opioids are transmitted faster in descending inhibitory pathway.

Another salient part of descending inhibitory pathway is serotoninergic NRM-spinal neuron. Serotonin was suggested as an analgesic transmitter in an early study [14], and EA can activate these serotoninergic NRM neurons [21]. This analgesic effect of EA diminishes after p-chlorophenylalanine (serotonin synthesis inhibitor) injection [22]. Therefore, serotonin is pointed to a role of AA. Evidence suggests that serotonin level increases in spinal cord after EA [23] and that its precursor (5-hydroxytryptophan) responds to enhanced analgesia at 2 Hz EA [24].

As to a neurotransmitter, it is always important to understand its receptor subtypes. There are several serotonin (5-HT) receptor subtypes in CNS. The 5-HT1 and 5-HT3 subtypes locate in the spinal dorsal horn and their agonists have been found to reduce pain [25, 26]. The 5-HT1a subtype is also an autoreceptor within the NRM. Antagonists for different subtypes of serotonin receptors, namely 5-HT1a, 5-HT2 and 5-HT3, have been used to elucidate their roles in AA. It has been found that EA analgesia is blocked by 5-HT1a and 5-HT3 antagonists at both lower and higher frequencies; whereas, EA analgesia is enhanced by 5-HT2 antagonist at high frequency (100 Hz) [24]. The results form these serotonin studies demonstrated another frequency-dependent characteristic of AA and are supported by later studies [27, 28].

The exact effect of serotonin in spinal cord is to activate inhibitory interneurons postsynaptically via the serotoninergic NRM-spinal terminals. The enkephalin-containing inhibitory interneurons knock out/down nociceptive signals through μ/δ-opioid receptors on presynaptic Aδ and C-fibers (heterosynaptic plasticity)[29]. EA, both lower and higher frequencies, can activate this mechanism mentioned above through 5-HT1a and 5-HT3 receptors. In contrast, the 5-HT2 receptor subtype increases the transmission of nociceptive signal [26]. It is also an excitatory receptor in the cortex and the hippocampus [30]. Higher frequency EA might decrease the serotonin concentration within the cortex; therefore it acts as a sedative. As a result, higher frequency EA elicits analgesic effect via both the descending pain inhibitory pathway and the cortical modulation.

In conclusion AA is mediated by the arcuate nucleus-PAG-NRM-spinal cord [19, 31] and PBN-PAG-NRM-spinal cord axes [18, 32]. These axes are activated frequency-dependently by lower or higher frequency EA. By injecting dynorphin antiserum to PAG decreases the analgesic effect of higher frequency; in contrast, the β-endorphin antiserum decreases the analgesic effect of lower frequency EA [18]. In addition, higher frequency EA can further involve in cortical serotonergic transmission, along with the NRM-spinal pathway.

2.2. Current researches in hyperalagesia models

Synaptic plasticity is the central mechanism of several neurological physiology and pathology, such as memory formation, epilepsy and hyperalgesia. One pattern of synaptic plasticity is homosynaptic, which means the change is only within synaptic cleft. If the change involved a second synapse, it is a heterosynaptic pattern. Interneurons usually play important roles in a heterosynaptic synaptic plasticity. Since acupuncture has capability to modulate nociception through spinal cord inhibitory interneurons in SG, synaptic plasticity becomes an appealing subject to address AA. Chemical-induced local inflammation or inflammation came from nerve injury lead to a series of changes of peripheral and central sensitization (hyperalgesia),

including undertrophed and overtrophed changes (e.g. change of nerve growth factors; NGF) of nerve ending, of upregulating specific kinds of dorsal root ganglion (DRG) receptors, of long-term potentiation (LTP) and long-term depression (LTD) on spinal dorsal horn neurons [33]. Hence, more recently researches focus on the acupuncture-mediated synaptic plasticity and anti-hyperalgeic effect in neuropathic pain animal models [20, 34-37].

Nerve injury and following local inflammatory response induce cytokines (IL1, IL6 and TNF-alpha) and NGF, which are related to hyperalgesia [38]. NGF is the central mediator of peripheral sensitization. Binding with tyrosine kinase receptor A (trkA), NGF induces catastrophic cascade in DRG neuron. For example, NGF-induced over-expression of ASIC3 [39] and transient receptor potential valloid type 1 (TRPV1) [40] result in increased cation permeability on DRG cell membrane and spontaneous activation. Current research showed that lower frequency EA prevents NGF-induced trafficking of TRPV1 and Substance P (SP) from DRG to peripheral skin [41].

Interestingly, NGF also induces expression of peripheral opioid receptors on inflammatory nerve endings at late stage [42]. This seems to be a compensatory reaction which responses to hyperalgesia. In peripheral inflammatory tissue, immune cells express endogenous opioid and bind to opioid receptors on peripheral nerve endings [43]. Research showed that analgesia of EA is mediated by this inhibitory binding on nerve endings [36]. From Sekido's research, local blockade of opioid receptors decreased the analgesic effect of EA rather than systemic blockade. Therefore, in early stage of hyperalgesia, EA regulates NGF-mediated changes in peripheral tissues, whereas in late stage EA enhances opioid-mediated leukocyte-neuron interaction.

DRGs play an important role in peripheral sensitization. Up-regulating receptors such as purinergic receptor P2X3, Acid-Sensing Ion Channel 3 (ASIC3) and TRPV1 increase response of nociceptor to noxious stimulation [33]. Our study showed that acupuncture reverses the mechanical hyperalgesia in both carrageenan- and complete Freund's adjuvant (CFA)-induced mice model by attenuating expression of ASIC3 on DRG [37]. Other evidences have suggested anti-hyperalgesic effect of acupuncture through P2X3 [44], TRPV1 [45] and P35/P25 [46]receptors attenuation. These studies implied that acupuncture affects neuron sensitization at level of receptor proteins.

Within spinal cord, there are various inhibitory interneurons modulating the synaptic plasticity. For example, inhibitory enkephalinergic neurons increase after nociceptive stimulation [47]. This inhibition blocks the ascending nociceptive signal from peripheral Aδ and C-fibers, as well as regulates synaptic plasticity and LTP contributing to the development of hyperalgesia [33]. Evidences have shown that acupuncture reduces hyperalgesia through spinal dorsal horn interneuron. For example, in CFA- and paclitaxel-evoked hyperalgesia models, intrathecal injection of opioid receptors antagonist reverse the anti-hyperalgesia effect induced by acupuncture [36, 48, 49]. These evidences suggested that acupuncture elicits anti-hyperalgesic effect via opioid receptors. However, the roles of different opioid receptors (μ, δ and κ) are not identical in different animal models. In paclitaxel model, clear evidence has shown that 10Hz EA acts through all three opioid receptors but in CFA model EA, only through μ- and δ-opioid receptors [35, 48, 50]; This conflict implies that animal models, different

treatment protocols (timing of needling and selection of acupoints) and tools of assessment can influence the result even when the stimulating frequency is similar.

Ionotropic glutamate receptors (NMDA, AMPA and KA receptors) are involved in LTP in DRG. Prseynaptically tetanus burst opens the postsynapse NMDA receptors and influx of calcium through NMDA up-regulates expression of AMPA receptor. Spontaneous discharge of DRG neurons in hyperalgesia animal facilitates LTP [51]. Therefore, the dorsal horn neuron is more sensitive to glutamate after LTP. EA has been found to prevent LPT by down-regulating AMPA and NMDA receptors in SG [29]. Indirect evidences that excitatory amino acid antagonists can enhance the anti-hyperalgesic effect of EA also support glutamate receptor-mediated anti-hyperalgsia of acupuncture [52, 53].

In conclusion, acupuncture reverses hyperalgesia at both peripheral and spinal levels. The effect is multifactorial but mainly through regulation of synaptic plasticity.

2.3. The role of Central Nervous System (CNS) on acupuncture treatments

We have known from the previous two sections that AA is mediated by descending inhibitory pathway and synaptic plasticity, but how acupuncture activates them is still blurred. It is believed that the sensation of "De Qi" during acupuncture treatments is the major determinant of therapeutic effectiveness. "De Qi" is, not a pain sensation, characterized with numbness, dullness, soreness or heaviness, therefore the sensory cortex and related structures has been postulated contributing to activation of abovementioned mechanisms. According to our studies, acupuncture can alter the sensory processing in CNS. For instance, electrophysiological studies have revealed that needling at specific acupoints suppresses the sympathetic skin response [54], cutaneous reflex [55] and blink reflex [56] supraspinally. These results suggested that acupuncture doesn't change the monosynaptic reflex at the brainstem and spinal level. Indeed, utilizing auditory endogenous potentials (P300), we elucidated that cerebral cortex is the major location where acupuncture interferes sensory processing [57].

In consistence with our early electrophysiology studies, current functional magnetic resonance imaging (fMRI) studies have demonstrated the importance of cerebral cortex. Given the intricate theory of TCM and the complicated networks of the CNS, the complexness of physiological response of acupuncture is not surprising. Functional magnetic resonance image (fMRI) was once regarded as a novel tool to elucidate the CNS effect of acupuncture. Indeed, Ho's group suggested that certain brain regions were activated in experimental animals with point-specific property [58, 59]. In human subjects, needling at traditional analgesic points (ST36 and LI4) can enhance the signals of analgesic matrix (hypothalamus and nucleus accumbens) and reduce the signals of pain perception area (limbic system) [60]. However, some results cannot be duplicated due to the sophisticated data process and analysis for the blood oxygenation-level dependent (BOLD) signals. For example, conflict results arise from two studies that tried to elucidate acupoint specificity by analyzing BLOD responses to vision-related acupoints [61, 62].

Most of the early fMRI studies have analyzed neural activities in an acute and spatial pattern. Lin's group noticed that carryover effects of block design (on- and off-treatment) would

complicate the interpretation of acupuncture fMRI study [63]. Therefore, currently a group focuses on effects of acupuncture on functional connectivity on resting-state. They have found that acupuncture can exert sustained and specific effects on resting brain networks [4, 61, 64-66]. Among all the brain regions, anterior cingulated cortex (ACC) has been studied most extensively [65, 67, 68]. ACC has wide connection with other cortical region and hippocampus, amygdala and hypothalamus. Therefore it is correlated with memorial (hippocampus), affective (amygdala) and physiological (hypothalamus) components of pain [69]. Indeed, in a hyperalgesic animal model, destruction of rostral ACC eliminates the anti-hyperalgesic effect of acupuncture [67]. However, the role of whole cerebral cortex plays in AA is still inconclusive, more delicate electrophysiology and functional imaging studies are needed.

In conclusion, functional studies (electrophysiology and fMRI) have revealed extensive effect of acupuncture on cerebral cortex. However, it is still controversial whether this effect is specific to acupuncture or not.

2.4. The role of Autonomic Nervous System (ANS) on acupuncture treatments

Autonomic anti-inflammatory reflex elicited by acupuncture has been postulated by virtue of acupuncture's anti-inflammation effect and ability to poise autonomic nervous system (ANS). It has been showed that long term EA can regulate immune cells such as T and B cell in lymph nodes [70] and splenic natural killer (NK) cells [71] in mouse. Elimination of immune regulation by naloxone [71] implied EA as an opioid-mediated immune modulator. In hyperalgesic animal models, inflammatory responses (edema and hyperalgesia) reduced by EA [72-74] is also mediated by opioids [75]. However, the fact that local injection of naloxane isn't able to eliminate the immediate anti-inflammation effect of EA [73, 75] may imply a faster neuronal pathway way other than opioid-mediated one. Indeed, EA is capable to adjust inflammatory profiles in the CNS. In the hypothalamus, commonly regarded as homeostasis center, the expression of mRNA of proinflammatory cytokines by lipopolysaccharide stimulation is reduced after EA [76]. Proteomic analysis has revealed that inflammatory protein levels are normalized in the hypothalamus after EA stimulation [77]. Taken together, a CNS-mediated non-opioid anti-inflammatory effect of acupuncture is implicated.

Although hypothalamus-pituitary-adrenal axis has been implicated to mediate the anti-inflammatory effect of acupuncture [59, 76-79], current focus is more on ANS [3, 80] by virtue of its more immediate response to acupuncture. Many researchers have found that acupuncture can regulate the function of the ANS in different kinds of physiology parameters [81-84]. But our question here is whether ANS also mediates the anti-inflammation effect of acupuncture. In enodtoxin-induced sepsis model, survival benefits of EA are mediated by central muscurinic and peripheral nicotinic receptors [3]. This result demonstrated the involvement of cholinergic systems in EA-mediated anti-inflammation, congruent with previous study [27]. Among various cortical areas, ACC receives lots of cholinergic terminals. Thanks to the advent of fMRI, it is more feasible to assess the neural connection within CNS. Current study suggested that acupuncture, via prefrontal cortex (PFC)-perigenual ACC (pgACC)-arcuate-PAG axis, could regulate ANS in spatial pattern [68]. This axis has strong interconnection to descending

inhibitory pathways and may be the common pathway of analgesic and anti-inflammatory effect of acupuncture.

In conclusion, the anti-inflammation effect of acupuncture is evident. In terms of the overlapping between cholinergic reflex and descending inhibitory pathways, acupuncture is speculated to be able to activate cortical ANS centers such as PFC and ACC.

2.5. Effect of acupuncture on metabolism

Acupuncture effect on hypothalamus nucleus (i.e. arcuate) implies its homeostatic characteristic. In contrast to reductionism of early modern medicine, TCM views living organism in systemic way. Emphasis is placed on holistic treatment in TCM theory. Therefore, acupuncture effect on metabolism has been the central of attention in scientific world. Current studies have shown that acupuncture on spleen and stomach meridians can regulate appetite and body weight through central mechanism[85, 86]. Therefore, acupuncture has been regarded as a novel alternative for controlling metabolic syndrome.

Insulin resistance is the major alteration of non-insulin dependent diabetes mellitus (NIDDM, type II DM) and metabolic syndrome. A series of studies on diabetic animal model has proven anti-diabetes effect of acupuncture. CV12 (Zhongwan) is a common acupoint used to regulate digestive function. Fifteen Hz EA at CV12 had hypoglycemic effect in normal and model rats of non-insulin-dependent diabetes mellitus (Type II DM)[87]. Likewise in analgesia studies, this hypoglycemic effect is also mediated by opioid [88, 89] and serotonin [90]. Fifteen Hz EA at bilateral ST36 (Zusanli) can further improve insulin sensitivity [91] by lowering free fatty acid in model rats of insulin-resistance [92]. Our study has also revealed that EA at ST36 can modulate the blood glucose and increase metabolic rate in the cellular level [93]. These results imply the clinical feasibility of acupuncture treatment for metabolic syndrome.

3. Clinical trials in acupuncture treatment

3.1. Important precautions for acupuncture trials

Study design is very crucial for acupuncture trials. Randomized control trial (RCT) is the minimal requirement for any modern clinical trial. However, for acupuncture trials, other precautions should be considered. Current acupuncture trials have to follow the standards of reporting interventions in controlled trials of acupuncture (STRICTA) [94]. To evaluate the validity of any acupuncture trial, additional emphasis should be placed along with STRICTA. The first one is “blinding method”. Double-blinded RCT means neither practitioner nor patient is aware of the content of treatment. However, it is virtually impossible for acupuncture trial since the practitioner have to delivery acupuncture or sham treatment according to the protocol and group assignment correctly. Therefore, blind to assessor and patient is relatively more important in acupuncture trials to avoid bias.

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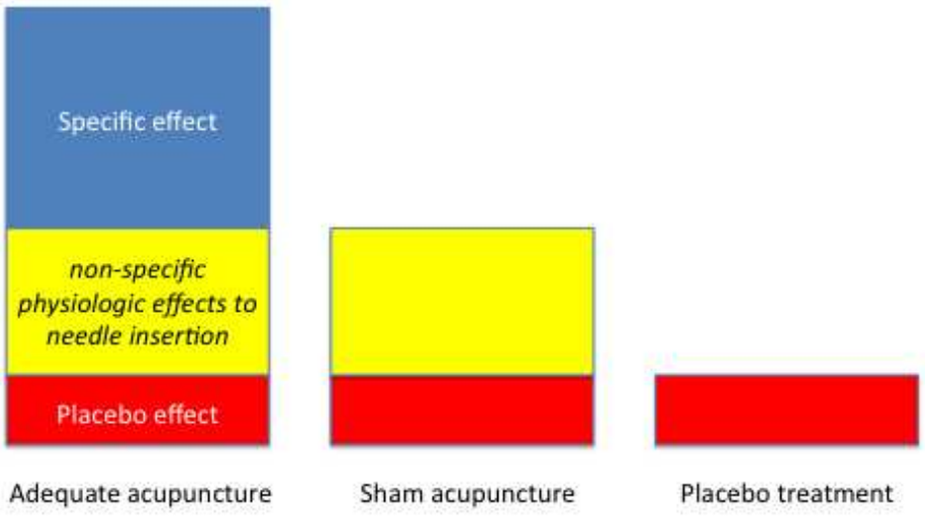

Figure 1. Three effects of acupuncture treatment. Left column is the three compositions of acupuncture treatment, namely, specific effect, non-specific physiology effect to needle insertion and placebo effect. Sham acupuncture such as minimal acupuncture (middle column) doesn't consist of specific effect. The right is placebo like mock TENS or Streitberger's placebo needles.

The second one is the design of sham treatment. It is commonly accepted that acupuncture has three major therapeutic characteristics (figure 1.), *point-specific effect, placebo and non-specific physiologic effects to needle insertion* [95]. Before going further into these three effects, two terms should be clarified ahead. Although often being used alternatively in many articles, the terms, sham acupuncture and placebo procedure, are not entirely equal in their meanings [96]. Pragmatically, sham acupuncture is defined as an ineffective and improper form of real acupuncture treatment. Sham acupuncture can elicit both the placebo and the non-specific physiologic effect to needle insertion. However, a placebo procedure should be really inert (namely, this procedure is not allowed to induce any physiological response, including the non-specific physiologic effect to needle insertion). Therefore, if a trial is to compare real acupuncture and blank negative control (no treatment control), the efficacy of acupuncture seemly cannot obtain conclusion (figure 2A). The therapeutic effect can either arise from *point-specific effect, placebo or non-specific physiologic effects to needle insertion* in acupuncture group. It is the usually case in early clinical trial. If a trial compared acupuncture with placebo treatment such as mock transcutaneous electrical nerve stimulation (TENS), then conclusion will be, at best, acupuncture elicits non-specific physiologic effects because, without needling, mock TENS cannot rule out the possibility of non-specific effect in acupuncture treatment. Only when a trial used minimal penetrating acupuncture at non-acupoints as sham treatment, then the therapeutic effect of real acupuncture can be deduced (figure 2B).

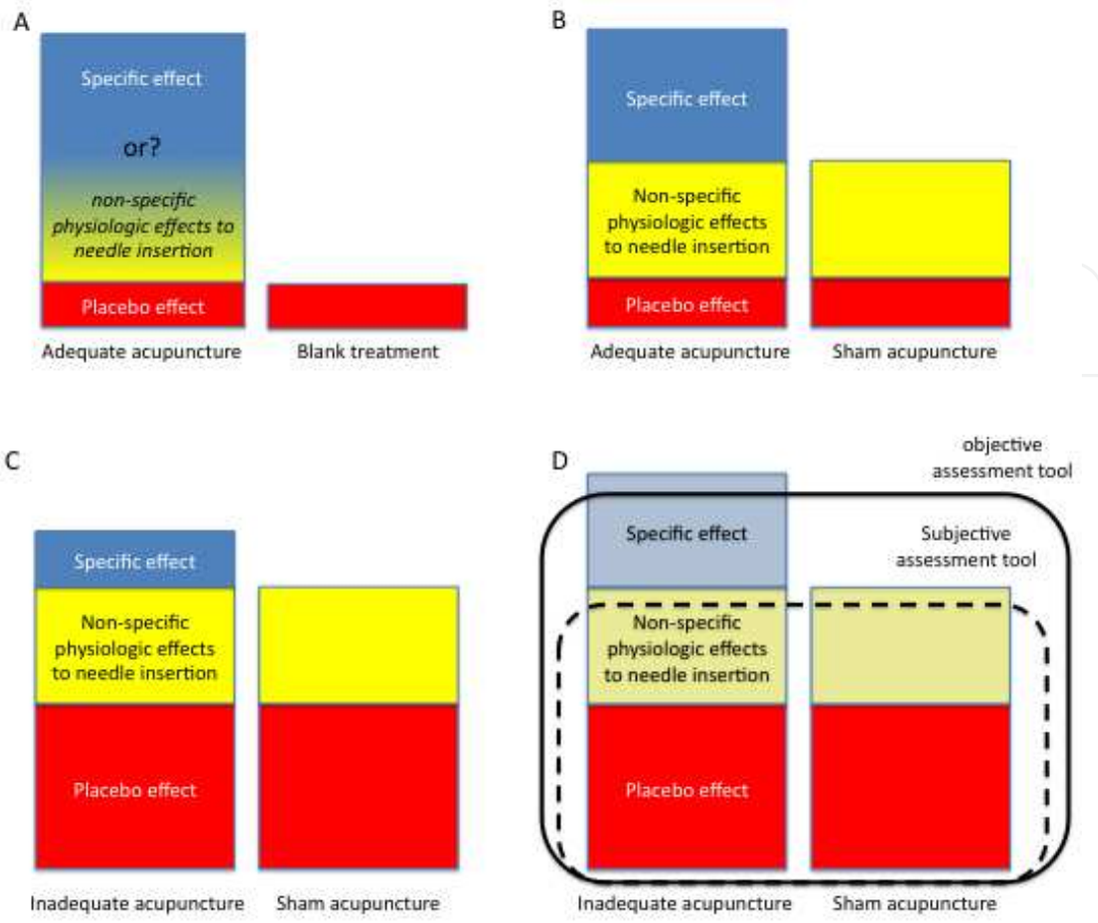

Figure 2. Different inadequacies jeopardize the RCT results. A, the lack of sham acupuncture makes assessment of real effect of acupuncture difficult. It is impossible to distinguish specific effect and non-specific effect of acupuncture without sham control. B, with sham acupuncture, the specific effect is more detectable. C, if the acupuncture treatment wasn't designed adequately, the specific effect of real acupuncture will be less significant along with the stronger placebo effects (the condition occurs often in migraine treatment). D, dashed line box is the area that subjective assessment tool (such as pain severity) can measure. Solid line represents the objective assessment condition. Without objective tool, specific effect could be ignored and significance between real and sham acupuncture vanish.

During early times, placebo effect of acupuncture is always a problem when it comes to clinical trials. As the advent of sham procedures and devices, how to diminish the non-specific effect of acupuncture dominates in modern acupuncture trials. One way is to maximally enhance the specific effect of acupuncture. Adequate point selection thus becomes important. For example, it happened in clinical trials to use identical acupoints for every patient in treatment group. Although it seems reasonable to do that, better choice is individualized acupoint selection according to meridian and TCM diagnosis. Otherwise, it will just like using penicillin for any pathogens in pneumonia cases. Inadequate point selection in real acupuncture treatment will obtain only non-specific and placebo effect, like minimal acupuncture (figure 2C). Above is the third precaution.

The final precaution is the outcome assessment, is especially important in analgesia trials. Because pain is a very subjective symptom and acupuncture is a time-consuming treatment,

http://dx.doi.org/10.5772/55184

placebo effect is usually amplified in both sham control and real acupuncture groups. If a trial only assessed the outcome by subjective method such as visual analog scale (VAS) and then the chance of overestimating placebo effect will increase and the chance to detect specific effect will decrease. This is especially true when an inadequate point selection occurs in a trial using minimal acupuncture as sham treatment (figure 2D). Therefore it is always important to assess outcome with objective parameters (such as range of motion or dosage of medication) along with objective ones (such as VAS or quality of life).

3.2. Pain syndromes

Pain syndromes are the most commonly conducted clinical trials using acupuncture all over the world because of the strong evidence of AA in experimental models. This section will only discuss some most-studied disorders, chronic headache, low back pain (LBP), osteoarthritis of the knee (OAK) and postoperative pain.

3.2.1. Chronic headache

Before the era of RCT, early non-randomized or non-controlled studies [97] have already found that acupuncture treatment can mitigate the severity and the times of migraine attack in a short- and long-lasting pattern. RCT further confirmed the efficacy of real acupuncture on an short- and long-term patterns [98] as well as its effect compared with conventional medication (metoprolol) [99]. However, like other early clinical trials, there are several inadequacies within these trials. For example, these trials are flawed by absence of concealment of allocation to groups and blurred explanation of dropout and withdrawal. These inadequacies make the result less convincing [100]. Another bias of early acupuncture trial is the lack of placebo or sham group, so that it had been assumed that acupuncture placebo effect dominates. Indeed, some researchers supported this assumption by their finding that acupuncture isn't superior to placebo [101-103].

In the introduction, we emphasize the importance of point selection. Originated from TCM, it would be better to choose acupoints according to TCM diagnosis and meridian theory. Therefore it is not surprising that some trials [101-103] concluded acupuncture as a placebo because of their point selection. For example, none of abovementioned studies used the TCM diagnosis (individualized assessment of patient's constitution regardless of their disorder) to choose acupoints. But if with individualized treatment, current trial conducted in Brazil was able to reveal better pain relieve during real acupuncture than minimal acupuncture [104].

Although it would be better to go according to TCM and meridian theory, it is very difficult to reproduce this kind of research conducted under the thinking process of TCM for its high experimental requirements and complicity [103]. Treatments delivered by different practitioners or strategies always result in different outcomes. Sometimes, it depends on how experienced the practitioners are; therefore current guideline (STRITCA) asks trialists to report the qualification of their acupuncture practitioners. Indeed, a previous trial found that acupuncture is a better preventive treatment for full blown migraine even in those patients who had previous received ineffective acupuncture therapy [105]. By treating those patients

within 48 hours after migraine attack, acupuncture can prevent mild migraine from exacerbating to full blown one. Interestingly, in this trial (n=179), most of the participants (80%) had previously received acupuncture for migraine without good success. This phenomenon confirms the idea that adequate trial design influences the trial result.

In conclusion, acupuncture is an effective tool to eliminate headache pain during attack and has short-term analgesic effect [106]. However, for lingering disorders like migraine, prevention is way more important than treatment for acute flare up. Acupuncture has been found to be more effective than Flunarize [107] and topiramate [108] for migraine prophylaxis. Although these studies revealed a positive result for acupuncture therapy, without an adequate sham or placebo design, it is still hard to elucidate acupuncture's real prophylactic effect from these studies. Indeed, one month after ending treatments, the difference between real and sham acupuncture on pain reduction and numbers of attack became insignificant [104]. Further well-designed trials are needed to elucidate the prophylactic effect of acupuncture on chronic migraine

There is no consensus as to whether acupuncture is superior to sham acupuncture for treating tension-type headache (TTH)[109]. Very few good quality trials have been conducted and their conclusions are conflicting. Different researchers can conclude even the same data differently. For instance, the result of one trial that implied no difference between real acupuncture and superficial acupuncture (at non-acupoit without De Qi) was conducted in 1992 [110]. However, later reviews reevaluated the data from the Tavola's study and found positive results favoring real acupuncture group [100, 111]. These reviews concluded that acupuncture was an effective strategy for treating TTH but they also pointed out the most difficult issue of acupuncture research is the placebo effect. Like migraine studies, some researches have concluded that acupuncture is a placebo [112, 113].

Since the placebo effect of acupuncture analgesia is difficult to retort in headache trials, researchers have tried to evade this effect by investigating the existence of any additional phenomenon of acupuncture. For instance, in Karsta's trial [114], they found that although acupuncture did not significantly decrease the severity of TTH attack in comparison to sham, it can objectively increase the pressure pain threshold. In other words, both groups felt the same degree of pain but acupuncture group had higher pain threshold. The explanation for this discrepancy between perception of pain and pain threshold is based on the strong placebo effect of real acupuncture. During the treatments, real acupuncture and sham acupuncture can reduce the perception of pain, in part mediated by placebo effect. It is especially the case because TTH is related to emotional stressor and both treatments can offer participants a relieved experience. But if this placebo effect is stronger enough in both treatments, then the specific effect (decreased pain threshold) of real acupuncture will be masked by placebo due to sampling and statistic limitation. This again reinforces our precaution that subjective parameters (pain severity) should be assessed along with objective ones (pain threshold).

Applying this conclusion to the migraine research, it is easily to speculate that there are certain specific therapeutic effects of real acupuncture causing objective changes in the patients with migraine, as the change of the pressure pain threshold in patients with TTH treated by real acupuncture. Indeed current trial suggested real acupuncture changes heart rate variability

(HRV) despite there are no significant difference in pain severity between placebo and real acupuncture [115]. Although this HRV change isn't easily correlated to migraine, ANS alteration may reflect hormonal, hemodynamic, electrophysiological or neural changes that can influence migraine.

In conclusion, acupuncture is effective in treating chronic headache. Because chronic headache may have psychogenic symptom component, the benefit of acupuncture might be partly contributed to the placebo effect of acupuncture; however, acupuncture dose elicit specific therapeutic effects that sham acupuncture dose not produce. Future trials should focus on develop objective assessment tools.

3.2.2. Lower back pain

Low back pain (LBP) may be the most popular pain condition for acupuncture trials. Although LBP is a self-limiting disease [116], it is a major cause of medical expenses, absenteeism and disablement [117]. Acupuncture is one of the most common complementary therapies for LBP. Early RCTs showed that acupuncture is superior to no treatment [118-120] in the pain scores, the dosages of pain pills, the limitation of activity and total hours of pain per. However, these early trials possess many serious flaws, such as poor description of statistical analysis and study protocol (including point selection, duration, interval, stimulation type and so on), small patient numbers, and unclear outcome measurements. As in chronic headache, these kinds of problems perplex most early clinical trials [121]. In these early clinical trials, we can also notice that the validity of a trial is correlated with the results. More valid the trials are, more likely the negative results are shown [122]. Therefore, again, it had been speculated that acupuncture is placebo effect [123]. However, current meta-analysis showed encouraging result of acupuncture treatment for patient with chronic LBP. Immediately after treatments, patients received acupuncture significantly had better reduction in pain intensity than placebo group [124]. However, long-term benefit cannot be observed in this meta-analysis. More RCTs may be needed to clarify the long-term effect, but more rigid design is equal important, especially for "point selection" and "outcome assessment".

Interestingly, compared with minimal acupuncture, individualized point selection in acupuncture treatment elicited better result in pain reduction [125]; whereas fixed point brought out non-superior pain reduction [123]. In both studies, acupuncture was used as a supplement to standard treatments. The phenomenon that acupuncture at individualized acupoints was more effective than minimal acupuncture but equal result of acupuncture at fixed point and minimal acupuncture implies the importance of strong non-specific and placebo effect of minimal acupuncture and fixed point strategy. Chronic LBP is not a specific diagnosis; it may consist of different disorders in different trials. If adequate acupuncture treatment cannot be given, non-specific and placebo effect then head up.

Outcome assessment by VAS and functional disability is still prevalent in acupuncture RCTs. However, the following example will ascertain again the importance of objective assessment tool. Being conducted in Germany [126] with considerable large numbers of volunteers and a firm methodological design, this research had been a strong cons of beneficial effect of acupuncture. The researchers aimed to determine whether acupuncture has a better thera-

peutic effect for chronic LBP than the minimal acupuncture (sham) and no treatment. After a long period of follow-up (8, 26 and 52 weeks) and with multiple measurements of outcomes (VAS; SF-36, 36-Item Short-Form Quality of Life Questionnaire; SES, Schmerzempfindungsskala (questionnaire for assessing the emotional aspects of pain); ADS, Allgemeine Depressionsskala (depression scale)), they concluded that acupuncture is better than no treatment but not better than sham acupuncture in pain relief. Only slightly improvement (compared with sham acupuncture) in functional outcome (SF-36 and times of limited function) in the acupuncture group was observed between baseline and follow-up periods. However, read it details, a significant pain relief of acupuncture treatment will be found if according to the need of medication in their discussion portion. Acupuncture group need less medication and has better functional outcomes than sham one. Dose that turn out to be strong pros of beneficial acupuncture effect?

Another interesting question is how long the acupuncture analgesia can last. According to a 2-years follow-up study, acupuncture can induce an analgesic effect in chronic LPB patients for at least 2 years [127]. Furthermore, an observational study [128] investigated the patients' outcomes after acupuncture. This observation included a total of 2564 patients treated by 1607 practitioners. It was shown that both functional outcomes and pain severity improved. In addition, the study also suggested that acupuncture could prevent LBP change to a chronic state.

In conclusion, acupuncture is a valid strategy for chronic LBP treatment. It can reduce the severity of and improve the functional outcomes in patients. Acupuncture seems to be a specific treatment rather than a placebo, although some authors do not agree. Combination of acupuncture and conventional interventions is a better choice for patient with chronic LBP.

3.2.3. Osteoarthritis of the Knees (OAK)

In TCM, OAK has long been treated by acupuncture. The major discomforts associated with OAK are pain and dysfunction of movement. Early pilot study revealed that acupuncture relieved pain and improved function in patients with OAK [129]. A later small RCT (n=73) confirmed that acupuncture group is superior in pain and functional outcomes to standard care group, even 4 weeks after treatment had been terminated [130]. However, take the non-specific and placebo effects into account, these results aren't convincing.

It is worth mentioning an interesting sham treatment used in Berman's trial [131]. First, they used plastic guidance tubes to mask their procedure. With the plastic tubes covering the true acupoints on the skin, the participants, who had never undergo prior acupuncture therapy, were not able to tell whether or not the needles were being inserted. In the acupuncture group, the needles were inserted (with De Qi sensation); in the sham group, the needles were not inserted. In addition to acupuncture at the acupoints that are commonly used for relieving knee pain, the researchers also needled at distal sham points on the abdomen that did not correspond to knee pain. The sham points were also covered by plastic guidance tubes. In the acupuncture group, the needles were not inserted into the sham points, whereas in the sham group, the needles were inserted into. Therefore, in the acupuncture group, the patients received real needling at the true acupoints and sham needling at the sham points; in the sham group, the patients received sham needling at the true acupoints and real needling at the sham

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points. In this crossover way, they can investigate effects of both placebo (true acupoints without needling) and non-specific physiologic effects to needle insertion (sham acupoints with needling) at the same time. The study comprised a total of 570 patients randomized into 3 groups, true acupuncture, sham acupuncture and education. Treatment was tapered over 26 months (2 treatments every week for 8 weeks; 1 treatment every week for 2 weeks; 1 treatment every 2 weeks for 4 weeks; and 1 treatment per month for 12 weeks). After a long period of follow-up (26 weeks post-baseline period), there are still 142 and 141 participants available in the acupuncture and sham groups, respectively. Most of the participants in both true and sham acupuncture groups reported that they had received true acupuncture. This suggested that this sham treatment is a credible blinding procedure and this sham acupuncture might elicit a similar degree of placebo effect as true acupuncture. Those who were received true acupuncture experienced better pain and functional outcomes; however, a significant difference in pain relief between the groups was not observed until 14 weeks. This implies that true acupuncture improves short-term and long-term functional outcomes, whereas the analgesia effect takes longer time to be elicited.

Other studies also suggested similar results that acupuncture is a benefit to the patients with OAK; however these studies showed that acupuncture can also elicited a short-term analgesia effect [132, 133]. These conflicting results might be due to the different placebo procedures or different treatment protocols.

In conclusion, although few reported discouraging results [134, 135], most of the trials published so far have shown preferable result of real acupuncture, especially in short-term pain and functional outcomes [136]. It is worth noting that, unlike acupuncture for chronic LBP, there is a general consensus among most studies that acupuncture is an effective treatment for OAK. Furthermore, its effectiveness (both in pain relief and functional improvement) seems not caused by the placebo or non-specific effects. This difference in effectiveness between these two diseases (LBP and OAK) might be due to the characteristics of the diseases. LBP is a heterogeneous syndrome comprising various disorders; it is an ambiguous and indistinct term. In contrast, OAK is a relatively clear and precise term to LBP. The diagnosis of OAK needs to meet many clinical criteria including imaging findings. Accordingly, there is less heterogeneity in OKA population than LBP.

3.2.4. Post-operative Pain

The prototype of modern acupuncture analgesia research is the minor surgeries such as thyroidectomy under acupuncture anesthesia performed in Mainland China [137]. Although in some recent reports it did not achieve excellent result [138, 139], this issue still fascinates researcher to assess the difference of anesthesia dose between acupuncture and control group [140, 141]. It has been shown that the fentanyl dose for anesthesia maintenance is significant lower in patient group who also receive auricular acupuncture than sham one [140]. Instead of acupuncture anesthesia, it is more common to use acupuncture as painkiller after surgery (post-operative pain). Previous trials have shown both equivocal [142] and negative results [143] of acupuncture for post-operative pain relieving. A more rigorous trial has demonstrated that acupuncture elicited a short-term analgesia effect in patients after oral surgery [144]. In

that study, acupuncture group received real needle treatment with De Qi needling sensation. Those in the placebo group were not needled, but instead received treatment with discernible tapped sensation by plastic tube on the area next to the acupoints chosen in the acupuncture group. In this way, the feeling that they have been treated in the placebo group can produce a placebo effect on them. Significantly longer post-operative pain-free period; delayed for sensing moderate pain and the need for the first dose of rescue pain medication was observed in the acupuncture group. However, these effects did not last longer than one week. This phenomenon suggests that acupuncture can elicit a short-term analgesic effect, in consistent with other pain syndromes. The acupuncture treatment timing for postoperative pain control is another interesting issue that has been studied in two different trials. In detail, these two trials were conducted by needling at similar acupoints (local ST6 and ST7 and distant LI4 among others) and a similar stimulation (manual acupuncture to achieve the De Qi sensation) but their results are opposite. Ekblom's trial has shown that there is no different of pain severity between the acupuncture and placebo group. The most obvious difference in study design between these two trials is the timing of intervention. The optimal timing of acupuncture are shown to be immediately after an operation [144] rather than before or 2-4 hours after an operation. A pretreatment of acupuncture attempted to prevent post-operative pain of oral surgery is in vain and as well as delayed acupuncture [143]. Based on the above study, we can assume that the timing of acupuncture intervention determined its analgesic effect on post-operative pain.

Acupuncture analgesia has also been studied in patients after the major abdominal surgery and it has been suggested that preoperative EA elicited no preventive analgesia after hysterectomy [142]. In this study, EA (100 Hz) was begun 20 minutes before skin incision and maintain until the end of the operation; the patients in the control group did not receive EA. The authors found no significant differences between two groups in pain severity, analgesics requirement and patients' stress states. However, this result is not consistent with a latter findings that shown the total amount of morphine [145] or fentanyl [146] required for pain control was significantly less in patients who received preoperative acupuncture than in patients in the control group. In Lin's trial, there were four groups included (control group without needling, sham EA group with needling but no electric stimulation, low-EA group with 2 Hz electric stimulation and high-EA with 100 Hz) and acupuncture treatment was performed 20 minutes before the induction of anesthesia. The analgesic effect is significant in patients who received higher frequency EA.

The conflict between these three trials can be contributed to the timing of intervention again. According to section 1 in this chapter, acupuncture analgesia is mediated by the regulation of CNS; however, under anesthesia, the CNS might not be able to activate neuronal and hormonal systems, which are correspond to acupuncture analgesia. In Christensen's study EA started after induction of anesthesia; therefore the analgesia effect of acupuncture may be reduced or eliminated by anesthesia. However, In Lin's and Coura's studies, acupuncture was performed before induction of anesthesia in order to elicit reliable CNS reactions.

Transcutaneous nerve electric stimulation (TENS) is a procedure that the electrodes are directly stuck on the skins. Although, the possible mechanism of TENS was found to be different from

that of traditional acupuncture or EA [147], we still can compared a study using TENS with Lin's [145] study to clarify the role of electric stimulation plays in analgesic effect. TENS at specific acupoints (ST36) has been shown to be more effective at inducing analgesia than TENS at non-acupoints after lower abdominal surgeries [148]. This phenomenon suggested that the analgesic effect is determined by the location the stimulation is given instead by electric stimulation that we apply. Therefore, we can speculate that both sham EA and real EA at non-acupoints cannot induce an effective analgesic effect as that in Lin's study [145].

Taken together, acupuncture and TENS at specific acupoints may provided a valid strategy for post-operative analgesia. The best timing to introduce acupuncture is 20-30 minutes before induction of anesthesia in major abdominal surgery and immediately after oral surgery.

3.3. Metabolic syndrome

Using acupuncture and herbal medicine to control weight is very popular in oriental countries. The beneficial effect of acupuncture on metabolism drives clinicians to conduct clinical trial on weight reduction and hypertension. There are two different methods of acupuncture for weight reduction, somatic (body) and auricular (ear) acupuncture. Both of them have their advantages. For example, somatic acupuncture is claimed to be able to enhance local fat metabolism [149], and auricular acupuncture is more convenient in clinical practicing. Indeed, crossover and pilot trials have documented benefit effect of EA on body weight (BW), BMI and waist circumference (WC) in obese women [150, 151]. Bimodal somatic acupoints, including CV6, CV9, ST28, K14 locally on abdomen and ST36, ST40, SP6 distally on legs, were chosen according to TCM theory in these trials. The effectiveness of this kind of bimodal point selection strongly implied the involvement of the CNS and related homeostatic nuclei (activated by diatal acupoints) in additional to focal metabolic effect (activated by local abdomen acupoints). As to auricular acupuncture, assumed mechanisms for weight reduction are involved the ANS (sympathomimetic effect) [152], leptin and ghrelin[153]. However, there is no RCT to verify the acupuncture effect on weight loss and we are suggesting future RCTs to compare the effect of either local (abdomen) or distal (leg, arm, aricular) acupoints roles.

3.4. Neurological disorders

Since major effective site of acupuncture stimulation is the brain, it has been used for treating neurological diseases other than pain. One of the popular topics is the effect of acupuncture treatment on stroke rehabilitation. For example, early trials have suggested that electric stimulation at some acupoints enhanced the neurological function in patients with hemiplegic stroke [154] and spinal cord injury[155]. Further RCT implied more balance improvement in stroke patients treated by true manual acupuncture [156]. Compared with control group who received acupuncture treatment without the sensation of "De Qi", true manual acupuncture at GV20 (Baihui) and 4 Spirit acupoints elicited an immediate effect on several balance parameters. It is important to understand the effect of stimulation modalities. In animal study, optimal scalp EA (5-20Hz) can increase blood flow during acute infraction, reduce infraction area and restore blood flow after acute infraction [157]. Our previous animal studies have revealed that EA at ST36 (Zusanli) increased the cerebral blood flow (CBF) in cerebral ischemia rats [158].

Acupuncture at GV20 (Baihui) enhanced the dopamine level and protected the neurons from apoptosis in the ischemia-reperfusion injured brains of rats [159]. Consistently, RCT also suggests scalp EA (2Hz) but not sham EA, improve functional outcomes after acupuncture [160]. It seems that adequate stimulation protocol is the major determinant of acupuncture treatment effect for ischemic brain injury. For example, RCT using 100Hz scalp EA cannot produce superior functional recovery in stroke patients compared with mock TENS [161].

In addition to scalp acupuncture, EA (1Hz) at cognition-related acupoints enhanced the cognitive function in patients with stroke [162]. Lin's group concluded that EA at PC6 (Neiquan) and HT7 (Shenmen) shown a promising effect for rehabilitation in stroke patients. Taken together, acupuncture treatments have benefit effects on the ischemic brain.

Another common acupuncture indication is peripheral neuropathy. As mentioned in previous section (see Current researches in hyperalgesia models), EA can attenuate hyperalgesia at peripheral and central level. Current research showed acupuncture can reduce severity of neuropathic pain in different neuropathies [163-165], but another sham control trial didn't support acupuncture [166]. More RCTs are needed to elucidate the real effect of acupuncture on peripheral neuropathies.

3.5. Asthma and atopic diseases

Anti-inflammation effect of acupuncture through ANS and immune systems make it a possible treatment for atopic diseases such as asthma, allergic rhinitis and eczema, but only few trials have been published in asthma [167, 168], allergic rhinitis [169] and eczema [170], therefore no conclusion can be made so far. However, in Scheewe's trial, acupuncture can improve rehabilitation response and the peak expiratory flow variability differs significantly, which means that acupuncture seems able to stabilize asthmatic airway. Further RCTs are needed to elucidate acupuncture effect on asthma.

4. Conclusion

From basic studies on AA to RCTs, current acupuncture researches illustrate us the diversities and possibilities of this traditional medicine playing an role in modern medicine. Commonly accepted by western countries, acupuncture studies first began at analgesia. The analgesic effect may be originated from cerebral cortex, brainstem, spinal dorsal horn, DRG to peripheral tissues. The study of the acupuncture mechanism and exact pathway are still in process. However, involvement of AAC, hypothalamus, PAG, NRM is more evident to date. Inhibitory interneuron and ANS are current focuses on acupuncture research. Results form these studies to date have shown effects of acupuncture on synaptic plasticity and cholinergic reflex. The clinical trials of pain syndromes have offered different level of evidences to support basic studies on AA. Short-term pain relief can be observed in migraine, chronic low back pain, post-operative pain and osteoarthritis of the knee. The effect of acupuncture seems longer in osteoarthritis and low back pain.

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Since CNS has been long believed to initiate acupuncture effect, functional studies such as fMRI and electrophysiology have been utilized to test it. The results confirmed the crucial role of CNS on acupuncture-mediated therapeutic effects. But it is also suggested some limitations of these tools. For example, spatial analysis of brain activity by fMRI is not as adequate as analysis of brain network connectivity. As to clinical trials, stroke is a current concern. Many trials suggested better functional outcomes in stroke patients treated with acupuncture. The effect is frequency-dependent, lower frequency (1-5 Hz) EA is more effective.

Diabetes and obesity are two major modern healthy issues all over the world. In animal models, the acupuncture effect on blood glucose is mediated by serotonin and endogenous opioids. The influence of acupuncture on metabolism also occurs at cellular level. Therefore, it is believed acupuncture can enhance metabolism in general and it has been used as a tool for weight reduction. Currently, no rigid RCTs available to verify the real effect of acupuncture on body weight. So is true for Asthma. Preliminary report suggested acupuncture can stabilize airway, but, like weight reduction, the effect is still unclear in the lack of rigid RCTs.

5. Summary

Being one of the major categories of complementary and alternative medicines (CAMs), acupuncture might be the most explored one. Despite current acupuncture researches have explored more diverse phenomenon such as anti-inflammation and regulation of homeostasis, neural system is still the main target. Early studies suggested that the central opioids and serotonin mediate analgesic effect of acupuncture. Current studies further illustrated the roles of synaptic plasticity and cholinergic reflex in acupuncture treatment. It is believed that acupuncture is able to modulate hyperalgesia and inflammation at levels of receptor proteins. Although the central nervous system (CNS) has been studied extensively, acupuncture effect on cerebral cortex is still in the scientific spotlight. Function imaging and electrophysiology studies have shown complicated networks that acupuncture involves in. Take the whole CNS into account; axes composing certain CNS regions are activated by acupuncture. For example, the anterior cingulated cortex (ACC)-arcuate-periagueductal gray (PAG)-nucleus raphes magnus (NRM) axis participates in analgesic effect of lower frequency electroacupuncture (EA).

Series of studies consolidated the beneficial effect of acupuncture on animal model of diabetes that blood glucose and insulin statuses are influenced by EA. These effects are also partly mediated by opioid and serotonin. In real clinical setting, acupuncture is used for weight reduction rather than for diabetes. Some current trials have validated its effectiveness as to weight reduction. Clinical trials on pain syndromes, stroke, neuropathy and asthma also have revealed different degrees of benefit of acupuncture treatment. Clinical research work on acupuncture has been carry on for many decades, most dominant in pain syndromes, namely chronic headache, low back pain, osteoarthritis and post-operative pain. However, some study result may possess inadequacies, such as fixed acupoint selection and the lack of objective assessment.

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