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The Status and Future of Acupuncture Mechanism Research

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Abstract

On November 8–9, 2007, the Society for Acupuncture Research (SAR) hosted an international conference to mark the tenth anniversary of the landmark NIH [National Institutes of Health] Consensus Development Conference on Acupuncture. More than 300 acupuncture researchers, practitioners, students, funding agency personnel, and health policy analysts from 20 countries attended the SAR meeting held at the University of Maryland School of Medicine, Baltimore, MD. This paper summarizes important invited lectures in the area of basic and translational acupuncture research. Specific areas include the scientific assessment of acupuncture points and meridians, the neural mechanisms of cardiovascular regulation by acupuncture, mechanisms for electroacupuncture applied to persistent inflammation and pain, basic and translational research on acupuncture in gynecologic applications, the application of functional neuroimaging to acupuncture research with specific application to carpal-tunnel syndrome and fibromyalgia, and the association of the connective tissue system to acupuncture research. In summary, mechanistic models for acupuncture effects that have been investigated experimentally have focused on the effects of acupuncture needle stimulation on the nervous system, muscles, and connective tissue. These mechanistic models are not mutually exclusive. Iterative testing, expanding, and perhaps merging of such models will potentially lead to an incremental understanding of the effects of manual and electrical stimulation of acupuncture needles that is solidly rooted in physiology.

Introduction

In November 8–9, 2007, the Society for Acupuncture Research (SAR) hosted an international conference to mark the tenth anniversary of the landmark NIH [National Institutes of Health] Consensus Development Conference on Acupuncture. This paper summarizes important invited lectures from the SAR conference in the area of basic and translational acupuncture research. Two companion manuscripts have been written in parallel and appear in this section of the issue. One covers clinical research (Park et al., 2008, pp. 873–883), and the other presents overviews of qualitative studies, the impact of the 1997 NIH consensus conference, and future directions in acupuncture research (MacPherson et al., 2008, pp. 885–889). In this paper, individuals who delivered lectures on basic and translational acupuncture research and have provided the summaries have been listed as coauthors.

Ahn discussed the scientific assessment of the acupuncture point and meridian. Longhurst described the neural mechanisms of cardiovascular regulation by acupuncture. Lao discussed mechanisms for electroacupuncture (EA) applied to persistent inflammation and pain. Stener-Victorin outlined basic and translational research on acupuncture in gynecologic applications. Napadow discussed how functional magnetic resonance imaging (MRI) has been used to evaluate mechanisms of acupuncture action. Harris focused on functional neuroimaging of acupuncture in fibromyalgia. Finally, Langevin delivered an overview lecture, titled "Acupuncture Basic Research: How Do We Put It All To-

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gether?" While this summary does not cover every development in basic acupuncture research in the past 10 years, many of the important advancements that have led to a better understanding of acupuncture mechanisms were indeed covered by the invited speakers. Through continued research into the mechanisms subserving acupuncture's clinical effects, we will be able to optimize and apply acupuncture to the clinical conditions, which may benefit most from this ancient therapeutic system.

Scientific Assessment of the Acupuncture Point and Meridian (Ahn)

The anatomical and physiologic nature of the acupuncture point/meridian remains elusive. Our limited understanding, however, is not for lack of existing hypotheses. Numerous physiologic and anatomical associations have been proposed within the literature. This summary provides a brief review of the scientific assessment of the acupuncture point and meridian. The discussion is limited to reported associations that (a) reflect common belief, (b) are sufficiently specific to the acupuncture point and meridian, or (c) are supported by more than 2 good-quality studies. With this critera, the talk focuses on two anatomical associations (nervous system and connective tissue), and three physiologic associations (trigger point, nuclear tracer migration, and electrical properties) are discussed.

Neural correlates reported in the literature include large peripheral nerves,[1] neurovascular bundles,[2] motor points,[3] mechanoreceptors,[4] free nerve endings,[5] and neuromuscular attachments.[1] The studies were performed predominantly in the 1970s and 1980s and were generally poor in quality. These studies lacked appropriate controls, had small sample sizes, and lacked detailed descriptions of acupoint localization. Overall, no macroscopic anatomical neural structure was clearly linked with acupuncture points.

The most recent anatomical association reported in the literature is the intermuscular/intramuscular loose connective tissue. According to recent studies, many acupuncture meridians and points align with intermuscular and intramuscular tissue.[6] Additionally, the collagen within the loose connective tissue may account for the needle-grasp effect reported at acupuncture points.[6–8] The biomechanical implications of this association are evolving, although the physiologic and clinical significance are yet unclear.

The analogy between trigger points and acupuncture points became widely discussed since Melzack et al.'s landmark study in 1977.[9] There are a number of similarities between the two: the two structures have similar locations; needles are used at both points to treat pain; the pain associated with the local twitch response at trigger points is similar to the *de qi* sensation; and the referred pain generated by needling trigger points is similar to the purported propagated sensation along the meridians. However, the acupoints located at these trigger points are not frequently used by acupuncturists and do not share the same clinical indications as the trigger point therapy.[10] Trigger points may represent a subset of acupuncture points—specifically, the *ah shi* points.

Nuclear tracers have been used to track the trajectory of acupuncture meridians in both humans and dogs. In most cases, ^{99m}Tc, in the form of sodium pertechnetate, was injected at low electrical resistance points to a superficial depth of 3–5 mm. The tracer migrated along the course of meridian at a rate of approximately 3–5 cm per minute.[11] For areas where the tracer was injected at nearby controls, the migration was not observed.[12] According to various experiments, this phenomenon is not directly attributable to veins or lymphatics although the interpretation of the results remains controversial.[11]

The electrical characteristics of acupuncture points and meridians are the most widely studied physiologic association in the literature. Acupuncture points have been reported to be local electrical resistance/impedance minima with diameters of approximately 1–4 mm. Acupuncture meridians have been reported to have lower electrical impedance and higher capacitance compared to adjacent controls. A systematic review of this literature suggests that there is insufficient evidence to support the electrical association, although these data are suggestive.[13] Interestingly, a significant proportion of studies on the anatomical and physiologic nature of acupuncture structures have used low electrical resistance points as a surrogate for acupuncture points.

Our understanding of the anatomical and physiologic nature of acupuncture points and meridians remains insufficient. The scientific characterization of these acupuncture structures is critical for the proper execution of a clinical trial—this characterization determines the proper localization of controls and helps identify the optimal therapeutic intervention. Further attention is needed to address this relatively neglected area of research.

Neural Mechanisms of Cardiovascular Regulation by Acupuncture (Longhurst)

There is evidence from a series of clinical trials for reduction in myocardial ischemia in patients with coronary disease and there are more variable data for acupuncture's ability to lower blood pressure (BP). For the last decade, scientists at our laboratory have sought to understand the signaling events and neurobiologic actions of acupuncture's regulation of the cardiovascular system better. Our initial studies, published in the late 1990s, indicated that acupuncture was capable of reversing demand-induced myocardial ischemia in a feline model of partial coronary ligation.[14] This action of acupuncture involved Group III and IV somatic afferents and the endogenous opiate system, which lowered myocardial oxygen demand by reducing reflex-induced increases in BP.[15,16] Subsequent studies demonstrated that both μ and δ-opioid, but not κ-opioid receptors in the rostral ventrolateral medulla (rVLM) were involved in acupuncture's action in the brainstem.[17] These studies, supported by immunohistochemical confocal microscopy,[18] therefore suggest that β- endorphin, endomorphin, and enkephalin, but not dynorphin, act as modulatory neuropeptides in this region during acupuncture. More recently, we have shown that nociceptin and gamma aminobutyric acid (GABA) are involved in inhibition of visceral reflex-induced increases in blood pressure following 30 minutes of low-frequency EA at P5–P6 acupoints, located over the median nerve on the forearms.[19,20] In our experimental models, we have demonstrated that low-frequency (2–4 Hz) but not high-frequency (20–100 Hz) EA effectively stimulates somatic afferents to provide input to regions such as the rVLM that regulate sympathetic outflow.[15,21] Our studies have also examined the concept of point specificity with regard to acupuncture's ability to lower elevated BP.[21–23] Using a positive and a negative electrode connected to needles at two adjacent acupoints, we have demonstrated that acupoints P5–P6, LI10–LI11, LI4–LI7, and St36–St37 effectively lower BP, whereas LI6–LI7 and G37–G39 are ineffective.[22] The extent of BP depression is dependent on the extent of convergent input to premotor sympathetic neurons in the rVLM. Simply placing a needle in an effective acupoint without mechanical or electrical stimulation did not influence elevated BP, suggesting that either needle placement without stimulation or electrical stimulation of an inactive acupoint can serve as adequate sham-control interventions,[15] Carefully comparing 2 Hz electro- and manual acupuncture showed similar lowering of reflex elevations in BP of approximately 40% with both interventions. Recently, we have begun to identify other regions, including the arcuate nucleus in the ventral hypothalamus and the ventrolateral periaqueductal gray (vlPAG) in the midbrain that constitute parts of a long-loop pathway activated during prolonged (10–30 minutes) somatic afferent stimulation with EA at P5–P6.[24–25] Our data show that the arcuate is an important source of opioid peptides that are transported to other regions such as the rVLM,[26] whereas the vlPAG is a known cardiovascular-depressor region. Stimulation of the median nerve, underlying P5–P6, increases activity in the arcuate, which through its projections, provokes activity in the vlPAG. The vlPAG either directly or indirectly provides inhibitory input to the rVLM to ultimately modulate premotor sympathetic outflow. Immunohistochemistry and microdialysis combined with electrophysiology have shown that sympathoexcitatory visceral reflexes stimulate premotor glutamatergic neurons in the rVLM that are modulated during EA through an opioid mechanism, because the process is blocked by microinjection of naloxone.[27,28] Furthermore, EA at P5–P6 frequently induces prolonged inhibition of rVLM premotor sympathetic neurons, lasting for more than 90 minutes.[29] This prolonged neuromodulation depends on an intact arcuate nucleus, and both opioids and GABA, but not nociceptin, systems in the rVLM.[19] Several of our studies have shown that acupuncture does not reduce BP in normotensive human subjects or experimental preparations.[30] However, in addition to acupuncture's BP-lowering effects, recent intriguing preliminary studies suggest that acupuncture also may be able to raise BP after it has been lowered reflexly.[31] Thus, we are beginning to understand the central neurocircuitry and neurotransmitter mechanisms underlying acupuncture's ability to lower BP in hypertensive states. These studies may have clinical utility for treating patients with hypertension, myocardial ischemia, and perhaps even congestive heart failure—all of which are associated with heightened sympathetic tone. Future studies will be directed at identifying still other regions in the brainstem, such as the medullary raphe nuclei, particularly the nucleus raphe obscurus, in addition to the nucleus tractus solitarii, the nucleus ambiguus and the dorsal motor nucleus of the vagus, as well as the many interactions among these nuclei that, together, modulate autonomic outflow and, hence, cardiovascular function during acupuncture.

Electroacupuncture Mechanisms on Persistent Inflammation and Pain (Lao)

Chronic or persistent inflammatory pain animal models, produced by inflammatory agents such as carrageenan and complete Freund's adjuvant (CFA), induce inflammation lasting for hours or days, respectively, and have recently been used to study the mechanisms of EA. During the past 8 years, scientists in our laboratory have been investigating mechanisms of EA antihyperalgesia and EA anti-inflammation in a CFA-induced persistent inflammatory pain rat model.

In the behavioral tests on this animal model, we observed that the effect of EA is parameter-dependant. EA at 100 Hz has a potent and short-term inhibitory effect on hyperalgesia but little effect on inflammation, while 10 Hz of EA has a moderate and prolonged antihyperalgesic effect as well as an anti-inflammatory effect.[32,33] Furthermore, our studies also demonstrate that the effect of EA on hyperalgesia and inflammation is mediated by two distinct pathways.

The hormonal pathway

EA anti-inflammation is mediated by hypothalamus–pituitary–adrenal (HPA) axis activities, as demonstrated by several lines of evidence: (1) At the adrenal level, EA treatment significantly elevated plasma corticosterone levels and decreased paw edema compared to sham EA. This antiedema effect was eradicated in animals given an adrenalectomy (ADX) and in those pretreated with a corticosterone antagonist RU486,[34,35] but neither treatment blocked the antihyperalgesia effect of EA. (2) At the pituitary level, EA significantly increased plasma adrenocorticotropic hormone (ACTH) levels, while the ACTH receptor antagonist $ACTH_{(1124)}$ blocked EA antiedema but not EA antihyperalgesia (unpublished data). (3) At the hypothalamus level, a corticotropin-releasing factor (CRF) receptor antagonist, astressin, blocked EA antiedema but only partially blocked the effect of EA antihyperalgesia (unpublished data). We also found that EA did not increase plasma corticosterone (CORT) and ACTH levels in naive rats, which suggests that EA affects healthy and pathologic conditions differently.

The neural pathway

At the spinal level, EA significantly inhibited CFA-induced *Fos* expression in the spinal dorsal horn, particularly at laminae I-II.[34,35] Pharmacologic studies showed that EA antihyperalgesia is mediated by mu and delta but not kappa opioid receptors.[36] Studies also show that lesioning of the G-protein-coupled receptor by pertussis toxin blocks EA antihyperalgesia.[37] Specifically, lesioning of mu receptor–containing spinal neurons with dermorphin-saporin shows this effect.[38] Furthermore, a dorsolateral funiculus lesion in the lower thoracic spinal cord significantly diminishes the effect of EA antihyperalgesia.[39] At the supraspinal level, EA activates *Fos* expression in the nucleus raphe magnus and locus coeruleus.[39] Our immunochemistry double-staining data show that EA specifically activates serotonin- or tyrosine hydroxylase–containing neurons in these nuclei, which project to the spinal cord.[39]

In conclusion, the rat persistent inflammatory pain model has provided an ideal animal model for investigating the effect and mechanisms of acupuncture on inflammatory pain and has produced data with potential clinical relevance for the treatment of chronic inflammatory pain. EA antihyperalgesia and antiedema are parameter-dependent and, moreover, are mediated via two distinct pathways. EA-produced antihyperalgesia is mainly mediated by sensory nerve pathways involving both spinal and supraspinal mechanisms, while EA-produced anti-inflammatory effects are mainly mediated by activation of the HPA axis.

Acupuncture in Gynecology (Stener-Victorin)

Female infertility—basic and clinical studies

Despite the lack of a large body of evidence —we cannot ignore the fact that many women receive acupuncture treatment to address infertility issues. Whether there is a true effect within the area of infertility or not, is a compelling reason for the scientific community to investigate. Acupuncture is a safe intervention in the hands of competent practitioners. In this sense, special acupuncture training in the area of women's health is essential.

Recent basic and clinical research demonstrate that acupuncture regulates uterine[40] and ovarian blood flow,[41,42] that the effect most likely is mediated as a reflex response via the ovarian sympathetic nerves, and that the response is controlled via supraspinal pathways.[41] It is important to point out that these studies show that the effect of acupuncture, at least partially, is mediated via sympathetic nerves but shed no light on the role of acupuncture in infertility treatment.

Acupuncture in endocrine and metabolic disorders

Polycystic ovary syndrome (PCOS) is the most common endocrine and metabolic disorder—"the female metabolic syndrome"—associated with ovulatory dysfunction, abdominal obesity, hyperandrogenism, hypertension, and insulin resistance. The precise etiology of the disease is unknown but excessive ovarian androgen production and secretion seem to play a key role. A potential contribution of the sympathetic nervous system as a primary factor in the development and maintenance of PCOS has been suggested.[43] We have conducted a study on women with well-defined and diagnosed PCOS and anovulation to elucidate the effect of repeated low-frequency (2 Hz) EA treatments on endocrinologic and neuroendocrinologic parameters as well as on anovulation.[44] This study showed that repeated low-frequency EA treatments exert long-lasting effects on both endocrinologic parameters as well as on anovulation. These results are in accordance with previous studies,[45,46] but it is obvious that randomized, comparative studies are needed to verify these results. However, these studies do not enlighten possible underlying mechanisms of EA, but it can be hypothesized that these EA effects are mediated through inhibition of the activity in the ovarian sympathetic nerves.

In recent studies on an estradiol valerate (EV)–induced rat polycystic ovary (PCO) model, we showed that repeated low-frequency EA treatments resulted in a reduction of high ovarian nerve growth factor (NGF), corticotrophin-releasing factor, and endothelin-1 concentrations—all markers for sympathetic activity—as well as increased low hypothalamic b-endorphin concentrations and immune function.[47] We have tested the hypothesis further that repeated low-frequency EA treatments as well as physical exercise modulates sympathetic nerve activity in rats with steroid-induced PCO by studying the expression of mRNA and proteins of α_{1a}- α_{1b}- α_{1d}- and β_2-adrenoceptors and the NGF receptor $p75^{NTR}$ and immunohistochemical expression of tyrosine hydroxylase (TH).[48] Physical exercise almost normalized ovarian morphology and both EA and physical exercise normalized the expression of NGF and NGF-receptors, as well as α_1- and α_2-AR, suggesting that these interventions may have a therapeutic effect.

Recently, our group developed a new rat PCOS model that incorporates ovarian *and* metabolic characteristics of the syndrome.[43] After continuous exposure to 5α-dihydrotestosterone, from prepuberty until adult age, the rats have typical PCO with an increased number of apoptotic follicles. Moreover, the rats develop obesity accompanied by enlarged adipocyte size and insulin resistance, indicating that high levels of androgens induce alterations in body composition and reduced insulin sensitivity in this PCOS model. What is of great importance is that we have shown that low-frequency EA *and* exercise ameliorate insulin resistance in rats with PCOS.[49] This effect may involve regulation of adipose-tissue metabolism and production because EA and exercise each partially restore divergent adipose-tissue gene expression associated with insulin resistance, obesity, and inflammation. In contrast to exercise, EA improves insulin sensitivity and modulates adipose-tissue gene expression without influencing adipose tissue mass and cellularity.

These rat PCO/PCOS studies demonstrate that low-frequency EA induces effects on the endocrine, the metabolic, and the sympathetic nervous system.[43]

Acupuncture in conjunction to in vitro *fertilization and embryo transfer*

Since the first publications reporting the use of acupuncture as an analgesic method during oocyte retrieval in *in vitro* fertilization (IVF) treatment,[50] and later studies investigating the role of acupuncture before, during and after embryo transfer (ET),[51] the clinical use of acupuncture has become widespread. These recent studies regarding the role of acupuncture in IVF/ET treatment, focusing on oocyte aspiration and ET, has been given much attention in debate and review papers.[52,53] Many of the trials are underpowered and the study designs among the trials differ, which makes it hard to interpret the data. However, the authors of a recent review concluded that current preliminary evidence suggests that acupuncture given before and after ET improves rates of pregnancy and live births among women undergoing IVF.[54] In this context, it is important to emphasize that, in a comment in the *British Medical Journal*, it is noted that a Danish randomized controlled trial (RCT) on adjuvant acupuncture that includes more than 600 women having IVF (twice as many as in the largest RCT included in the meta-analysis) is currently underway.[55] Before adding adjuvant acupuncture for IVF to any national guideline, we must wait for the results of this and other studies to clarify the value of this treatment.

In conclusion, it appears that acupuncture may have a beneficial effect on women with PCOS; this possibility is supported by both clinical and experimental evidence. However, there is a need for more RCTs on women with well-defined diagnoses of PCOS. The results indicate that low-frequency EA modulates sympathetic activity. Furthermore, acupuncture in conjunction with IVF/ET treatment might have a potential role but still there is a lack of clear evidence to support this possibility yet.

Evaluating Acupuncture with Functional Magnetic Resonance Imaging: From Characterization to Translational Research (Napadow)

Although animal research clearly supports a role for antinociceptive limbic, hypothalamic, and brainstem networks in acupuncture analgesia, these results must be placed in the context of more complex human cognition. One complementary approach to study neurophysiologic correlates of acupuncture in humans includes neuroimaging—mapping or localizing brain function.[56] A leading noninvasive neuroimaging method with good spatial and adequate temporal resolution is the hemodynamic-based functional MRI (fMRI), which can estimate activity anywhere in the brain every few seconds. The use of fMRI to study acupuncture has occurred since the mid-1990s and has included both characterization studies in which needle stimulation was performed during neuroimaging, as well as studies in which brain responses to conventional, well-characterized stimuli were evaluated both before and after acupuncture.

Characterization studies from several groups have demonstrated overlapping responses to acupuncture within multiple cortical, subcortical/limbic, and brainstem areas.[57–60] This should not be surprising as acupuncture is a complex somatosensory stimulus that is sure to elicit sensorimotor, affective and higher cognitive/evaluative processing. Regions include the primary and secondary somatosensory cortices (SI, SII), which support initial localization and early qualitative characterization of somatosensory stimuli. Limbic brain regions (e.g., the hypothalamus, amygdala, anterior cingulate cortex [ACC], and hippocampus) are also recruited, and probably mediate any affective/emotional response. Furthermore, many characterization studies have demonstrated modulation of the anterior and posterior insula, and the prefrontal cortex (PFC). The insula have been implicated in pain processing and may play a specific role for acupuncture,[61] while the PFC has multiple distributed connections with the limbic system and is likely to also play an important role in expectancy-related responses.[62]

Studies using fMRI have also investigated how acupuncture modulates well-characterized pain stimuli, nonpain somatosensation, and even resting brain function. For instance, we recently found that following verum, but not sham, acupuncture, there was increased resting functional connectivity between specific brain areas and the default mode network (DMN)—a network of brain regions more active during a nontask processing state, and thought to subserve interoception or self-referential cognition.[63] Specifically, postacupuncture, the DMN was more connected with pain- (ACC, periaqueductal gray [PAG]), affective- (amygdala, ACC), and memory- (hippocampal formation, middle temporal gyrus) related brain regions. These results demonstrate that acupuncture does not just affect brain function *during* needle stimulation but can enhance the poststimulation spatial extent of resting brain networks. This effect may play a role in acupuncture analgesia, which is known to develop after significant time delays.

Neuroimaging can also be coupled with longitudinal clinical evaluation, as we have done for carpal tunnel syndrome (CTS). After a 5-week course of acupuncture, patients with CTS had less hyperactivation to finger stimulation, and more focused SI finger representation.[64] Furthermore, we found that, compared to healthy adults, patients with CTS had more closely separated somatotopic representations for the second and third fingers (both median-nerve innervated).[65] After acupuncture treatment, the second and third finger representations were further apart, approximating the separation seen in healthy adults. Furthermore, we found that, compared to healthy controls, patients with CTS responded to acupuncture (at LI-4, distal to the lesion) with greater hypothalamic activation and more prevalent amygdala deactivation.[66]

In the future, characterization studies will continue to be important (especially in correlation with peripheral and clinical metrics), as we still do not know the "specific effect" of acupuncture. However, newer approaches to fMRI (e.g., functional connectivity) coupled with clinical evaluation will become more prominent in the coming years as we try to understand the mechanisms behind some of the ambiguous results (acup $\approx$ sham) from recent RCTs.

Functional Neuroimaging of Acupuncture in Fibromyalgia: Insights into Mechanisms and Clinical Trial Design (Harris)

Fibromyalgia (FM) is a common chronic pain condition that afflicts approximately 2%–4% of individuals in industrialized countries.[67] Although the underlying pathology of this condition is unknown, a disturbance in central neural function has been suggested. Research using fMRI has shown that brain regions known to process and modulate pain information have augmented activity in these patients.[68,69] More recently, positron emission tomography (PET), a brain-imaging technique that can be used to assess static and dynamic aspects of neurotransmitter systems, has been used to study μ-opioid receptor (MOR)–binding ability in FM.[70] MORs within the nucleus accumbens, the cingulate, and the amygdala show reduced binding ability in patients with FM. Because these receptors normally function to inhibit neural activity, these patients may have reduced inhibitory neurotransmission in pain-modulating brain regions.

Several clinical trials of acupuncture in FM have been performed to date; however, the findings have been equivocal, with most studies showing that acupuncture and sham acupuncture (SA) are equally effective for reducing pain.[71–73] As a consequence, the acupuncture field has had trouble separating acupuncture analgesic effects from placebo effects in FM. Neuroimaging methods such as PET may provide insights into this problem. Because MORs have been implicated in both acupuncture as well as placebo analgesia,[74,75] functional imaging of these receptors may provide information into acupuncture effects.

We utilized PET imaging to find out whether acupuncture and SA would have the same effects on central opioid receptors in patients with FM. Seventeen (17) patients with FM were randomized to receive either 9 traditional acupuncture (TA; n = 9) or 9 SA (n = 8) sessions over the course of 1 month. PET imaging and clinical pain ratings, assessed with the short form of the McGill Pain Questionnaire (SFMPQ), were performed pre- and post-treatment.

As expected there, was no difference in clinical pain reduction for both groups (SFMPQ total: MeanDiff (standard deviation) TA = 5.4 (9.6); SA = 2.3 (6.4); $p = 0.44$). However the two interventions had dramatically different effects on central MOR binding ability. In the insula, the amygdala, the thalamus, the cingulate (anterior and perigenual), the caudate, and the prefrontal cortex, TA caused an increase in MOR binding ability, whereas SA caused a decrease in receptor binding ability (all $p < 0.001$; uncorrected). These data suggest that, while acupuncture and SA have similar effects on clinical pain, their underlying opioid-receptor mechanisms are not equivalent.

Results from neuroimaging studies such as these have had minimal impact on clinical trials of acupuncture to date. If TA is not simply the sum of SA plus any specific needling effects, this finding has implications for the design of acupuncture clinical trials. One may not be able to assume that the effects of SA are embedded in the active treatment arm in the same way that "placebo effects" are thought to operate in the active arm of a drug trial. Replication and validation of these findings requires further investigation.

Acupuncture Basic Research: How Do We Put It All Together? (Langevin)

Although basic research on acupuncture has made considerable progress in the past 10 years, we still lack a clear picture of "how acupuncture works." An ongoing source of frustration, especially among practitioners of acupuncture, is that existing mechanistic models have tended to greatly "simplify" acupuncture. Although such models may apply to specific situations (e.g., obtaining immediate analgesic effects), it is not clear how they relate to acupuncture practice as a whole, which includes treatment of complex chronic conditions. An additional source of confusion is that the term "acupuncture" is used by some people to describe a variety of procedures performed at acupuncture points but not necessarily involving needles (e.g., "noninsertive" methods or laser stimulation), while other people define acupuncture is as a procedure involving the insertion of acupuncture needles, but not necessarily at acupuncture points. Despite these difficulties, mechanistic models are important as they provide a framework to test specific hypotheses. To be optimally useful, models need to have a well-defined scope and a solid physiologic foundation, and be testable, given currently available technology.

So far, mechanistic models that have been investigated experimentally have focused on the effects of acupuncture-needle stimulation on the nervous system, muscles, and connective tissue. By far, the most extensively tested model has been that of neural stimulation. Well-documented and reproducible effects on the peripheral, central, and autonomic nervous systems have been demonstrated for both manual and electrical stimulation with acupuncture needles in humans and animals. The relevance of these mechanisms to pain reduction, peripheral anti-inflammation, cardiovascular, gastrointestinal, and endocrine regulation are summarized in the preceding papers by Longhurst, Lao, Stener-Victorin, Napadow, and Harris. Another model that has received a substantial amount of attention is the "trigger-point" muscle stimulation model. Acupuncture needle manipulation can be used to stimulate hyperirritable foci at neuromuscular junctions causing a specific "twitch response" that can alter extracellular inflammatory mediators surrounding the trigger point, suggesting that this mechanism may be related to local pain reduction.[76] Finally, the connective-tissue stimulation model was based on the observation that manual stimulation with acupuncture needles causes highly specific mechanical stimulation of subcutaneous loose connective tissue. Fibroblasts within the loose connective tissue respond to this mechanical stimulation with active cytoskeletal remodeling that may have important downstream effects within connective tissue.[77,78] Although the relationship between these connective-tissue responses and clinical effects remains unknown, the intriguing overlap between acupuncture meridians and connective tissue suggests a possible relevance of this connective-tissue model to poorly understood Traditional Chinese Medicine concepts, such as propagation of effects along acupuncture meridians.[6] It is of course important to emphasize that these mechanistic models are not mutually exclusive. Iterative testing, expanding, and perhaps merging of such models will potentially lead to an incremental understanding of the effects of manual and electrical stimulation with acupuncture needles that is solidly rooted in physiology.

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