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Neural substrates, experimental evidences and functional hypothesis of acupuncture mechanisms

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Objectives – Although acupuncture therapy has demonstrated itself to be effective in several clinical areas, the underlying mechanisms of acupuncture in general and the analgesic effect in particular are, however, still not clearly delineated. We, therefore, have studied acupuncture analgesic effect through fMRI and proposed a hypothesis, based on the obtained result, which will enlighten the central role of the brain in acupuncture therapy. *Methods* – The proposed model, termed as a broad sense hypothalamus-pituitary-adrenal (BS-HPA) axis, was based on our observed neuroimaging results. The model incorporates the stress-induced HPA axis model together with neuro-immune interaction including the cholinergic anti-inflammatory model. *Results* – The obtained results coupled with accumulating evidence suggest that the central nervous system is essential for the processing of these effects via its modulation of the autonomic nervous system, neuroimmune system and hormonal regulation. *Conclusions* – Based on our fMRI study, it appears that understanding the effects of acupuncture within a neuroscience-based framework is vital. Further, we have proposed the broad sense-HPA axis hypothesis which incorporates the experimental results.

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As functional brain imaging techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have improved, there have been attempts to observe possible correlations between acupuncture stimulation and neural responses to demonstrate correlations between cortical activation and specific acupuncture stimulation (1–10).

With improved resolution and sensitivity of these brain imaging tools, better understanding of the mechanisms of acupuncture would certainly be possible in the near future and could provide us with a more clear and unambiguous picture hitherto unavailable by any other technique.

In this paper, we present some of the recent observations related to acupuncture or acupuncture-like stimuli and review recently evolving scientific aspects of acupuncture based on the evidences obtained by functional brain imaging (9–12), neurochemical studies (13) and neuroimmunophysiological studies (14–23). In addition, a hypothesis of the acupuncture mechanism is proposed based on previously available data and well-known models such as the stress-induced analgesia via the hypothalamus–pituitary–adrenal axis (HPA axis) (14–16), the neuroimmune interaction of the cholinergic anti-inflammatory activity (15, 17, 18), and our and other neuroimaging evidences (9–12).

Immune, neural stimulation and HPA axis hypothesis on acupuncture mechanisms

A recent series of studies conducted by Tracey and colleagues (15, 17, 18) describe the interaction

between the autonomic nervous system (ANS) and the immune functions and show how the brain communicates with these two systems. These studies provide interesting and important clues for the formulation and understanding of acupuncture mechanisms. For example, inflammatory information is transmitted through sensory nerves to the hypothalamus where input signals are processed; it then results in an anti-inflammatory output via the ANS. The thought that acupuncture might be involved as a modulator of the immune system has recently been supported by several observations and it has been suspected that acupuncture might affect immune modulation (19, 20). Although actual scientific evidence is yet to be scrutinized, studies concerning neuroimmunology and autonomic reflexes could form an important base for understanding of the basic acupuncture mechanism as a neural-immune reflex (14, 15). More specifically, tumor necrosis factor (TNF) and other cytokines [interleukin-1β (IL-1β) and high mobility group B-1] exist in the brain and directly interact with the inflammatory immune system. By communicating with the brain these cytokines stimulate neural outflows via the ANS (14–16, 18). Parasympathetic nerve endings release acetylcholine (ACh), and this resulting neuroimmune reflex appears to suppress release of the inflammatory cytokines (IL-1β). This cholinergic suppression of inflammatory cytokines is a new observation and could play an important role in understanding acupuncture mechanisms (15).

The dorsal vagal complex and the dorsal motor nucleus of the vagus nerve are also known to respond to circulating TNF concentrations and they activate the HPA axis thereby eventually inducing release of glucocorticoids, among others, which subsequently will suppress further cytokine synthesis (14, 15).

Based on Tracey's concepts of vagus nerve stimulation, combined with possible anti-inflammatory effects to the inflamed area (14, 15, 18), afferent somatic nerve stimulation can be another important component of acupuncture. In other words, the afferent visceral and somatic acupuncture signals can be transmitted to the supra-spinal level for the induction of the reflexive anti-inflammatory signals through both humoral and neural mechanisms (Fig. 1). Thus, a total of three different modes of acupuncture or acupuncture-like sensory stimulation can be involved:

1 AV-acupuncture (afferent vagus nerve-acupuncture or afferent vagus nerve stimulation);
2 EV-acupuncture (efferent vagus nerve-acupuncture or efferent vagus nerve stimulation); and

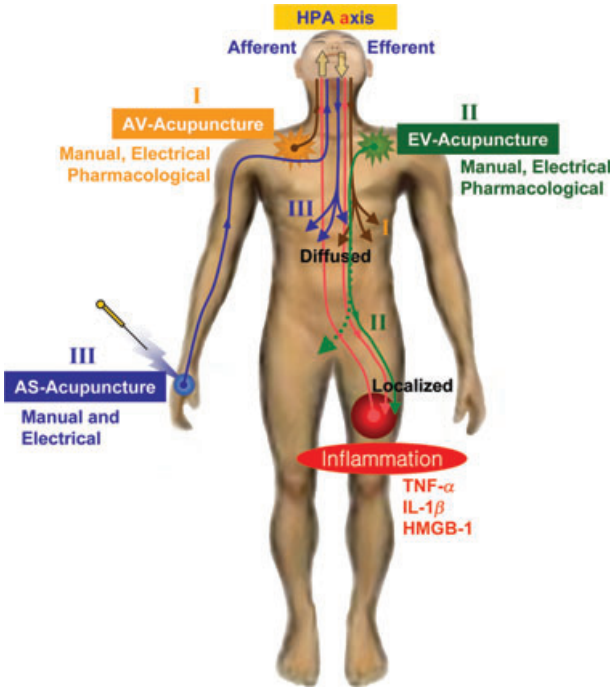

Figure 1. Afferents and efferents of the possible acupuncture pathways. By each different afferent and efferent stimuli, a number of distinctive descending reflexive and direct anti-inflammatory signals will be induced (first, see the basic efferent anti-inflammatory signal as a result of the localized afferent cytokine signaling of TNF, IL-1 and HMGB-I). As a result of acupuncture or acupuncture-like stimuli, three distinctive reflexes can be hypothesized: (i) efferent anti-inflammatory signal I with AV-acupuncture (afferent vagus nerve-acupuncture); (ii) direct efferent anti-inflammatory signal II with EV-acupuncture (efferent vagus nerve-acupuncture); and (iii) efferent anti-inflammatory signal III with the AS-acupuncture (afferent somatic nerve-acupuncture), respectively. HPA axis, hypothalamus–pituitary–adrenal axis; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; HMGB-1, high mobility group B-1.

3 AS-acupuncture (afferent somatic nerve-acupuncture or afferent somatic nerve stimulation).

From these different afferent and efferent stimuli, as well as the inflammation signal, a number of distinctive descending anti-inflammatory reflexes can be induced, which include:

1 efferent anti-inflammatory signal due to AV-acupuncture [via nucleus of solitary tracts (NST) and HPA axis];
2 direct efferent anti-inflammatory signal due to EV-acupuncture (via the dorsal motor nucleus of vagus); and
3 efferent anti-inflammatory signal due to AS-acupuncture (via other brainstem nuclei, other than NST, or via NST or both, as well as sympathetic outflow from the hypothalamus possibly via the broad-sense HPA (BS-HPA) axis).

As Tracey and his colleagues demonstrated, vagus nerve stimulation resulted in an increase of efferent vagus nerve cholinergic activity leading to an anti-inflammatory effect. These facts suggest that afferent AV-acupuncture would work similarly. However, the most often and widely used acupuncture stimulation appears to be the afferent somatic nerve stimulation (AS-acupuncture) by the insertion of acupuncture needles and twirling onto the cutaneous muscles. One could, however, expect that similar effects of AS-acupuncture might even induce broader and diffuse efferent nerve activities, covering both generalized sympathetic and parasympathetic nerve activities via the hypothalamus [see implication of the efferent sympathetic nerve activities at the end of the nerve terminals (15)].

Neural substrates and afferents to the paraventricular nucleus of the hypothalamus

To further substantiate the above discussion, it is worthwhile to look at the stress-related circuit that could provide important clues. The model most supportive so far is the stress-induced HPA axis model (16). We propose to extend this model to a BS-HPA axis. In this model, four major inputs to the paraventricular nucleus (PVN) of the hypothalamus are noted. These four inputs converge onto the PVN, from the group that consists of the limbic system and the prefrontal cortex (LIM), the circumventricular (CV) area, the sensory stimulation (SS) and the hypothalamus (HYP) itself. These four inputs together with various nuclei are possibly involved with activation of the classically known stress-induced HPA axis. Although inputs from the psychogenic, chemogenic and integrative components could play modulatory roles, as our discussion is on acupuncture, we will limit our discussion only to the sensory stimuli.

Acupuncture needling or acupuncture-like sensory stimulation (SS) can further be divided into three major inputs or afferents which all project to the PVN, possibly via activation of various neurons in the brainstem area. These pathways include: one from the body (somatic-body sensory afferent; SS-SBS); one from the head and facial regions (somatic-head and special sensory afferents; SS-SHS, which include even the visual and auditory pathways); and the visceral afferent (visceral or vagal sensory afferents; SS-VS). These are probably the acupuncture-related sensory stimuli that we term as 'neurogenic' components to differentiate from the visual and auditory aspects of SS-SHS.

Efferents (or outflows) from the hypothalamus (15, 16, 24–26)

Major efferents or outflow from PVN by acupuncture or acupuncture-like sensory stimuli may be conveyed via five distinctive pathways.

The first group of pathways (#1) is humoral, originating from the HPA axis and projecting to various organs in the body and the brain via the bloodstream. One of them is the pathway (#1′) to the inflammatory area where immune-related leukocytes, such as macrophages, are induced and the other is the pathway (#1″) to the supraspinal central nervous system (CNS), as shown in Fig. 2.

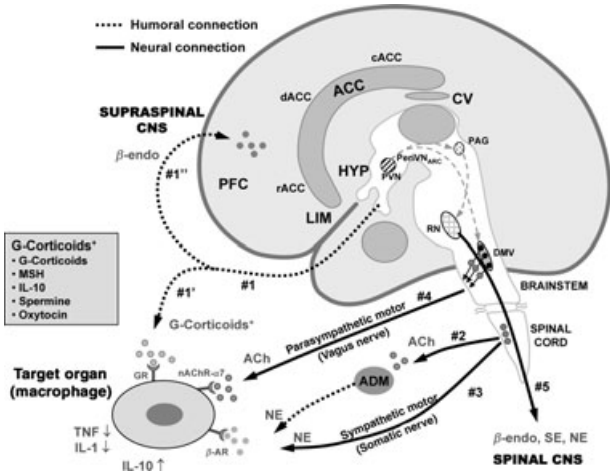

Figure 2. Five major efferents from the hypothalamic PVN related to the broad-sense hypothalamus–pituitary–adrenal (BS-HPA) axis which would have an effect on suppression of cytokines and pain at the inflamed areas as well as other central nervous system regions. This BS-HPA axis appears to play the key role in acupuncture. The humoral pathways (1 and #2) target to the macrophage in the inflammatory area and other diffuse areas of the higher brain, and release a number of anti-inflammatory cytokines and hormones which act on the macrophages as the suppressor of the inflammatory cytokines and also as a beneficial factor to other areas of the brain (for example β-endo). The neural pathways (#3 and #4) include both sympathetic and parasympathetic outflows which release NE and ACh. The last group of the pathway (#5) is neural and it appears coupled directly from the periventricular nucleus and possibly the arcuate nucleus of the hypothalamus, thereby forming the hypothalamus–PAG–raphe axis to the dorsal horn of the spinal cord where inhibitory action takes place. The later is the well-known central-descending pain-inhibitory pathway that inhibits the ascending pain signal from the periphery. ACC, anterior cingulate cortex; rACC/cACC/dACC, rostral, caudal and dorsal ACC; LIM, limbic system; CV, circumventricular organs; PFC, prefrontal cortex; ADM, adrenal medulla; ADC, adrenal cortex; HYPO, hypothalamus; PVN, paraventricular nucleus; $PeriVN_{ARC}$, periventricular and arcuate nucleus; PAG, periaqueductal gray; RN, raphe nucleus; DMV, dorsal motor nucleus of vagus; GR, glucocorticoid receptor; nAChR-α7, nicotinic ACh receptor α7; β-AR, β-adrenergic receptor; TNF, tumor necrosis factor; G-corticoids, glucocorticoids; IL-1, inteleukin-1; ACh, acetylcholine; IL-10, interleukin-10; β-endo: beta-endorphin; NE, norepinphrine; SE, serotonin.

The humoral pathway (#1′) targets the macrophages in the inflammatory area and releases a number of anti-inflammatory hormones such as glucocorticoids and anti-inflammatory cytokines such as IL-10. These hormones and cytokines reduce inflammation and pain. Another humoral pathway (#1″) is the β-endorphin-releasing pathway. It is conceivable that the HPA axis induces β-endorphin release thereby projecting to diffuse areas within the brain (see pathway #5). The second group (#2) is the hypothalamic autonomic sympathetic nervous (HAS) system-driven neurohumoral pathway releasing norepinephrine (NE), thereby suppressing inflammation by activation of beta-adrenergic receptor (β-AR) at the macrophage (15). This pathway is traditionally known to precipitate a number of adverse effects, such as increase of heart rate and vasoconstriction (15, 18). The third one is a neural pathway (#3), the noradrenergic sympathetic outflow, which probably originates from the HAS axis via the spinal cord. Here, again NE is released and expected to release IL-10 by activation of the β-AR similar to pathway #2. The fourth pathway (#4) is the hypothalamus autonomic parasympathetic (HAP) vagus nerve outflow, which is cholinergic. It is directed to macrophages and dendritic cells and interacts with nicotinic acetylcholine receptor, nAChR-α7, thereby suppressing the synthesis of TNF-α and IL-1β (15). The anti-inflammatory effect of this cholinergic pathway is newly discovered and strongly suggests that the resultant vagus nerve outflow activity, due to the afferent vagus nerve stimulation or other sensory stimuli, would be an important contributor to the anti-inflammatory activity and could be related to one of the beneficial effects of acupuncture or acupuncture-like stimuli (9, 10, 15, 22). The last pathway (#5) is neural and coupled directly from the periventricular nuclei and the arcuate nucleus of the hypothalamus to the periaqueductal gray (PAG), and then to the raphe nuclei and to the dorsal horn of the spinal cord. This neural pathway is the well-known central-descending-pain-inhibitory pathway in the spinal cord influencing the ascending pain signal pathway from the periphery (24). This pathway is of special interest, as its effect can be observed by neuroimaging in conjunction with acupuncture or acupuncture-like stimuli and pain as discussed below (9, 10).

Experimental evidences and hypothesis of acupuncture mechanism

Some of the recent experimental observations such as measured immune response, functional brain imaging using PET and fMRI and the existing physiological models can now be used to construct a rationale or a hypothesis of the mechanism of acupuncture.

Immune response by electroacupuncture (25)

First, an anti-inflammatory effect of electroacupuncture (EA) has been evaluated. Response of two different frequencies, i.e. low frequency (2-Hz group) and high frequency (100-Hz group), respectively, was measured 3 days after induction of acute pancreatitis by cholicystokinin (CCK) in a rat model. Stimulation was given once a day for 7 days, each with 20 min duration. The rat was killed at 12 h after the last performance. Thereafter, weight of pancreas, heat shock proteins (HSPs), β-amylase, lipase, IL-β and TNF-α were measured. Pancreas weight/body weight ratio (3.45 ± 0.51 in group I, 3.79 ± 0.23 in group II) was decreased significantly compared with the control group (4.61 ± 0.31). Expressions of HSP60 and HSP72 in both groups I and II were increased more than the control group, especially in group I. Both β-amylase and lipase were decreased significantly in groups I and II, while it increased significantly in the control group compared with the normal group. IL-1β release was decreased significantly down to 0.32 ± 0.16 and 0.98 ± 0.70 ng/ml, respectively, in group I and group II compared with the control group (1.74 ± 0.37 ng/ml) while it increased more than 10 times than that in the normal group (0.12 ± 0.13 ng/ml) (see Fig. 3A). In addition, TNF-α release was decreased to 41.71 ± 7.18 and 44.50 ± 10.15 pg/ml, respectively, in both group I and group II. The control group (50.50 ± 9.29 pg/ml) was increased more than the normal group (39.60 ± 11.87 pg/ml) (Fig. 3B). The above results strongly support our hypothesis that acupuncture stimulation changes the immune response, as evidenced by a decrease in proinflammatory cytokines.

Sustained pain increases release of endogenous opiates (11)

The most convincing evidence that supports the acupuncture mechanism is the μ-opioid-receptor studies in animal models (13) and more recently in the human brain (11). According to the study of opioid receptors in rat or human brain, receptors are distributed in specific areas such as the anterior cingulated cortex (ACC), the hippocampus and most parts of the thalamus (Fig. 4A). They vary with the diurnal rhythm affecting perception of pain, having an analgesic effect (26). In the human

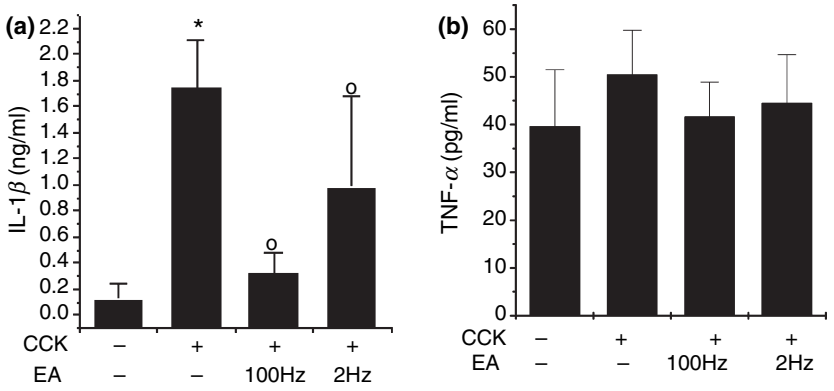

Figure 3. Effect of electroacupuncture (EA) on interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) secretion in cholicystokinin (CCK)-induced acute pancreatitis. Anti-inflammatory effect of EA (2 and 100 Hz) has been evaluated. Means ± SEM for five animals are shown. IL-β and TNF-α were measured on the third day after induction of acute pancreatitis by CCK in a rat model. $^{*}P < 0.05$ compared with the normal group.$^{\circ}P < 0.05$ compared with the control group.

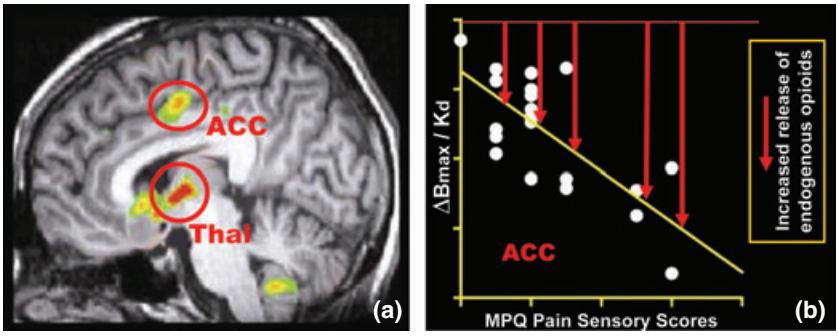

Figure 4. Regional μ-opioid-receptor regulation of sensory and affective dimensions of pain observed with C-11 Carfentail by positron emission tomography (PET). Change in activities in the ACC and the thalamic area, the major pain signal processing and relay stations, suggest that pain stress enhances the release of endogenous opioids at specific areas where pain signal processing is believed to occur, in this case, the ACC. This negatively correlated activity seen by PET with increasing pain stress score [McGill Pain Questionnaire (MPQ) score] suggests that there is an increased release of the endogenous opioids as a result of the sustained pain stress increases. Arrow represents amount of the increased release of endogenous opioids in average [courtesy Zubieta et al. (11)]. ACC, anterior cingulate cortex; Thal., thalamus; $\triangle B_{max}/Kd$, difference in endogenous opioid release or binding to the μ-opioid receptors between the baseline pain and the increased pain experiences as a function of MPQ pain sensory scores.

brain, the medial pain system is likely to be more susceptible to opioid modulation than the lateral pain system (27). A recent observation (11) by PET with the selective μ-opioid-receptor radiotracer, C-11 carfentanil, suggests that sustained pain, which is neurogenic (as acupuncture stimuli), produces an increased release of endogenous opioids, possibly via the BS-HPA axis (16), more specifically via the periventricular structures including the arcuate nucleus of the hypothalamus, thereby increasing the endogenous opioids at specific areas (Fig. 4) where pain signal processing is believed to occur, i.e. the cingulate cortex or the ACC, and the pain signal relay station, the thalamus (28).

Rostral ACC plays a critical role in pain modulation

Another interesting development in the horizon is the placebo (psychogenic) study reported by Petrovic et al. (12). In their study, an attempt was made to investigate the brain regions that are commonly activated during the placebo condition and during the administration of opioids. Interestingly, rostral ACC (rACC) was observed in both real-opioid (remifentanil, data not shown) and placebo (saline) conditions (Fig. 5A). The increased blood flow in the rACC with pain stimulation together with placebo suggests that the placebo induces endogenous opioids similar to the exogenous opioid administration (remifentantil). This increase of rCBF in the rACC is consistent with previous works (29, 30). A similar result has been observed in some pain studies by using fMRI (9, 10, 28), strongly suggesting the involvement of similar pain-processing mechanisms (Fig. 5B). In addition, activation of the rACC showed delayed response compared with other regions in the temporally resolved fMRI data, suggesting that the rACC has a functional role in pain modulation (28). This could involve various pain-coping strategies and the initiation of pain control in conjunction with other analgesia-modulating brain areas, such as the traditionally known PAG–raphe–spinal cord axis (27, 31, 32, 38). Indeed, Petrovic et al. (12) have also observed a

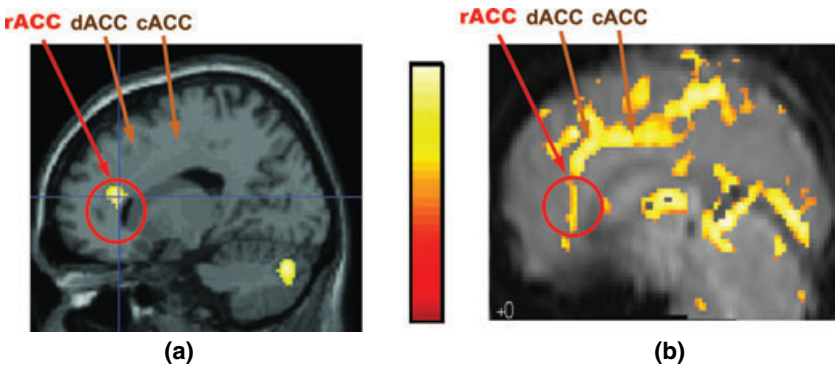

Figure 5. Placebo effect with pain and pain signal processing observed by positron emission tomography (PET) (12) and functional magnetic resonance imaging (fMRI) (10, 27). (a) Placebo effect with pain and resulting expression of opioids observed by PET. The increase in rCBF induced by placebo was similar to the one by real opioids in the pain-processing areas, such as the rACC and the PAG (data not shown). (b) Cortical activation due to pain stimulation observed by fMRI. Note the similarity in activation of the rACC in PET and fMRI suggesting that rACC is a possible pain-modulating center [courtesy from Petrovic et al. (12) and Cho et al. (10, 27)]. rACC/cACC/dACC, rostral, caudal and dorsal anterior cingulate cortex; PAG, periaqueductal gray.

covariation in activation between the rACC and PAG at the brainstem when the pain was administered under a placebo condition.

Both acupuncture and acupuncture-like stimuli decrease pain

Recent fMRI observations of acupuncture revealed several interesting results and provided clues about how basic acupuncture mechanisms might work (9, 10). Pain stimuli activated most of the known pain-processing centers in the study, such as the dorsal ACC (dACC), caudal ACC (cACC) and rACC together with the supplementary and premotor areas as well as the primary motor areas (28–30, 33, 34) (Fig. 6A). Thalamic areas are also activated robustly, as expected, as the thalamus is the main relay station of the pain sensory signal to the upper cortical areas including the cingulate cortex. These pain-related areas substantially decrease their activities after the administration of acupuncture (Fig. 6B). These changes of activation after the administration of acupuncture on the traditionally described acupoints (Meridian-acupuncture points) clearly demonstrate that the pain-processing areas are desensitized due to acupuncture stimulation. Interestingly, the same experiment but with Sham-acupuncture point stimulation instead of Meridian-acupuncture point, showed

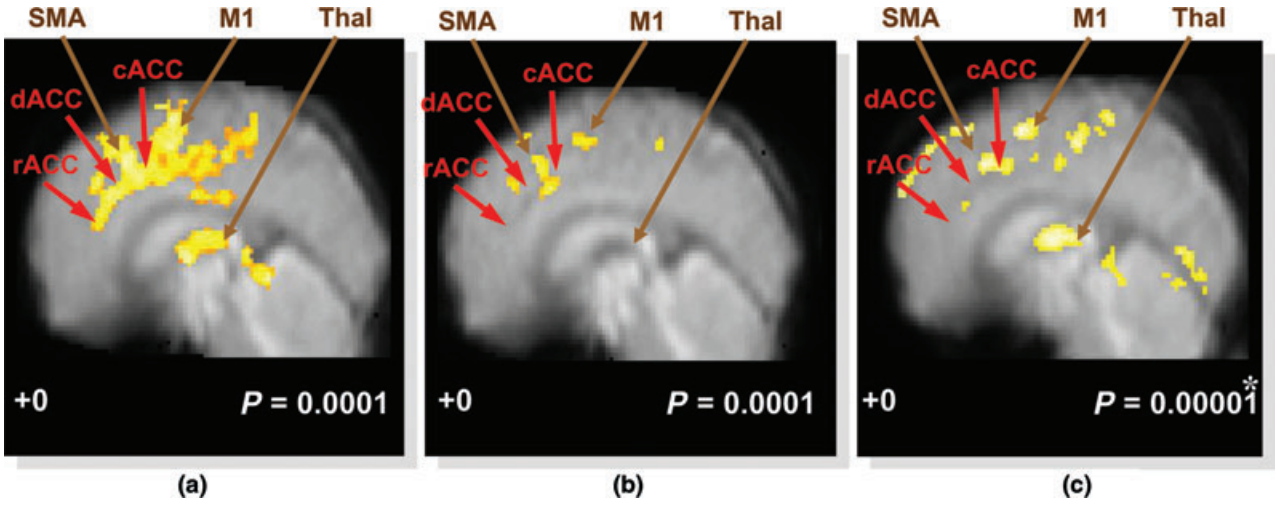

Figure 6. Comparison of the functional magnetic resonance imaging (fMRI) results of 'pain', 'Meridian-acupuncture + pain' and 'Sham-acupuncture + pain' experiments (10). (a) The cortical activation by pain alone clearly demonstrates that the pain indeed activates most of the known pain-processing centers such as the dorsal anterior cingulate cortex (dACC), the caudal anterior cingulate cortex (cACC) and the rostral anterior cingulate cortex (rACC) together with the supplementary motor and the primary motor areas. (b) An activation pattern resulting from pain stimulation after the administration of 'Meridian' acupuncture shows substantially decreased activity in most of the areas that were once activated by pain stimulation alone, namely, the dACC, the cACC and the rACC. (c) Same as (b) with 'Sham' acupuncture. This result appears nearly the same as (b). SMA, supplementary motor area; M1, primary motor; Thal, thalamus.

striking similarity in fMRI results (Fig. 6C). The Sham-acupuncture point was chosen deliberately away from the Meridian-acupuncture point and applied with an intensity of stimulation similar to that of the Meridian-acupuncture. This study suggests that acupuncture is effective in pain relief regardless of the choice of point, although there may be some differences in their efficiency (10). In fact, it supports the hypothesis that the effect of acupuncture, at least acupuncture analgesia, is simply the effect of the stress-induced HPA axis response mediated by stimulation resulting from acupuncture, i.e. decreased activation in pain-related areas may be due to '*sustained pain stress*' in any point on the body rather than a specific point stimulation as the traditional acupuncture school teaches. It implies that acupuncture or acupuncture-like sensory stimulation activates the HPA axis. Therefore, the endogenous central opiate circuitry (See Fig. 3) reduces or inhibits the ascending pain signals.

This is consistent with the data obtained by Zubieta et al. (11) and Petrovic et al. (12) as discussed below.

Discussion

There is an increasing number of new molecular and neurophysiological research reports in stress effect studies (14, 16, 35–37), anti-inflammatory immune response studies (15, 18) and neuroimmune-based acupuncture research (19, 20) and more recently neuroimaging-based acupuncture research (6–10). These reports strongly support the view that acupuncture mechanisms can be explained on molecular and neurophysiological bases, specifically via the BS-HPA axis mechanism. The BS-HPA axis hypothesis not only shares the well-known central-descending-pain-inhibitory theory involving endogenous opioids, but also suggests that there is a possible anti-inflammatory mechanism in conjunction with neuroimmune pathways and the cholinergic anti-inflammatory mechanism (13–15).

Among efferents from the hypothalamus, norepinephrine, which is the sympathetic neurotransmitter, can be proinflammatory in some scenarios, such as excessive sympathetic tones (38, 39). But, weak or adequate sympathetic responses, such as light exercise or acupuncture, suppress inflammation by releasing NE as stated above.

The mechanisms behind acupuncture treatment are on the verge of verification with the help of newly available molecular imaging tools such as the high resolution and high-sensitivity molecular-imaging PET and high-field fMRI. These imaging techniques enable us to investigate changes in both neurochemical and hemodynamic responses. With these scientific developments, it seems important at this point in time to investigate not only acupuncture but also various other modalities loosely related to acupuncture or acupuncture-like stimuli, such as sympathetic ganglion block and vagal nerve stimulation, as they are widely practiced in Western medical community (40).

Future acupuncture studies are needed to investigate various input parameters which can affect the outcome of acupuncture stimulation, such as stimulation intensity, frequency, duration of stimulation, the repetition rate, etc. In addition, various physiological differences, such as body constitution, pathological conditions and daily rhythm of humoral secretion (such as glucocorticoids) should also be considered as important parameters to which attention must be paid.

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