Acupuncture of LI-4 in Anesthetized Healthy Humans Decreases Cerebral Blood Flow in the Putamen Measured with Positron Emission Tomography

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To minimize the influence of exogenous factors, 13 volunteers were anesthetized with sevoflurane 1 MAC while exposed to manual acupuncture stimulation of LI-4 (Group 1, $n = 7$) or a placebo point in the space between the third and fourth metacarpals (Group II, $n = 6$). During anesthesia (baseline) and anesthesia + acupuncture, one $H_2{}^{15}O$ scan was performed, respectively. Group I demonstrated a significant decrease in regional cerebral blood flow in the right medial frontal gyrus (20%) and in the left putamen (17%). In Group II regional cerebral blood flow was decreased in the right medial frontal gyrus (22%); in the putamen no significant changes were observed. These data suggest that needle penetration of the skin affects the medial frontal gyrus, whereas acupuncture of LI-4 influences the putamen.

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Studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have demonstrated a broad cerebral response to analgesic acupuncture involving the limbic system and limbic-related brain structures, including the hippocampus, hypothalamus, nucleus accumbens, cingulate, insular cortices, cerebellum, caudate, and putamen (1–6).

PET and fMRI visualize brain activation in a variety of clinical conditions, but it is often difficult to relate these images to specific neurology when nonspecific effects of the treatment process also seem to influence brain activation (7). One study demonstrated that placebo analgesia is related to decreased brain activity in pain-sensitive regions, and that the effects of placebo analgesia are associated with expectation (8). In connection with placebo, an increased activity was demonstrated in the anterior cingulate cortex, insula, and thalamus during anticipation of pain, and decreased activity in expectation of pain relief (8). There seem to be substantial overlaps in the brain between the areas of placebo response and expectation and the areas responding to acupuncture.

To minimize the influence of exogenous factors we performed the present study in anesthetized healthy humans. PET was used to investigate changes in regional cerebral blood flow (rCBF) during manual acupuncture needle stimulation of LI-4 (Hegu acupoint). Acupoint LI-4 was chosen because it is the most frequently used in experimental studies of acupuncture analgesia.

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METHODS

Participants and Study Design

The study was approved by the Regional Committee on Ethics in Medical Research. All participants gave their written consent to participate in the study after the experimental procedure, and radiation effects had been extensively explained.

Thirteen right-handed, nonsmoking, healthy volunteers were enrolled in the study, seven men and six women (equal across the groups), median age 24 yr (range 21–27), and median weight 72 kg (range 55–92).

Before the examination, arterial and venous catheters were inserted in the left radial artery and right antecubital vein, respectively. Electrocardiogram, arterial oxygen saturation (Sao_2), end-tidal (ET) carbon dioxide, and ET sevoflurane concentrations were continuously recorded (AS3 Datex, Instrumentarium Corp, Helsinki, Finland). Noninvasive arterial blood pressure measurements were performed at 5-min intervals.

The participants received no premedication. Sevoflurane was administered in 40% oxygen via a tight-fitting facemask using a calibrated vaporizer through a non-rebreathing circuit. The target ET drug concentration was 1.0 MAC. To achieve steady-state cerebral concentrations, these ET concentrations were maintained at least 10 min before

Table 1. Arterial Blood Pressure, $Paco_2$, Bispectral Index, and Absolute Global Cerebral Blood Flow Values During the Baseline State (1 MAC Sevoflurane Anesthesia) and Acupuncture Needle State in Both Groups

	Group I ($n = 7$)		Group II ($n = 6$)	
Vital variables	1 MAC sevo	1 MAC sevo + acu	1 MAC sevo	1 MAC sevo + acu
Mean BP (mm Hg)	77 ± 7	74 ± 11	75 ± 6	72 ± 11
$Paco_2$ (kPa)	5.9 ± 0.5	6.3 ± 0.5	5.7 ± 0.4	6.1 ± 0.5
BIS values (0–100)	43 ± 2.6	39 ± 5.3	45 ± 3.1	41 ± 4.3
gCBF (ml/100 g/min)	57 ± 9.6	59 ± 8.4	55 ± 7.3	58 ± 7.4

BP = blood pressure, BIS = Bispectral Index, gCBF = absolute global cerebral blood flow.
All values are presented as group mean ± SD.

the PET scanning. The volunteers maintained spontaneous ventilation during anesthesia. To maintain a patent airway, assistance was sometimes needed. An increased ET carbon dioxide (>0.5 kPa) was the criterion for intervention.

The volunteers were anesthetized with 1 MAC sevoflurane while exposed to manual acupuncture needle stimulation of LI-4 (Group I, $n = 7$) or a nearby nonclassical/nonanalgesic point at the space between the third and fourth metacarpals (Group II, $n = 6$), on the right hand. The needle was inserted perpendicular to the skin surface to a depth of approximately 1.0 cm and rotated clockwise and counter-clockwise at a rate about 180 times per minute (3 Hz). The stimulation commenced 5 min before the injection of labeled water and lasted during the whole scan procedure. One CBF-PET scan was performed during the baseline state (1 MAC sevoflurane) and at 1.0 MAC sevoflurane + acupuncture. Immediately after each PET scanning procedure, an arterial blood sample was withdrawn and analyzed (ABL 300, Radiometer, Copenhagen, Denmark) for whole-blood acid–base variables.

Bispectral Index (BIS) was measured by a strip electrode (2000 Aspect Medical Systems; BIS sensor). The BIS-values were recorded continuously for each volunteer and registered after each scan image.

Magnetic Resonance Imaging

For the purpose of functional–structural correlation, high-resolution T1-weighted MRIs were obtained for each volunteer. A 3D fast spoiled GRASS sequence with 116 transaxial slices (1.5-mm slices, echo time 4.2 ms, repetition time 10.6 ms) was acquired using a 1.5 Tesla GE Signa MR scanner (GE medical systems, Waukesha, WI).

PET Assessments

PET measurements were performed using the ECAT EXACT HR (CTI/Siemens) whole-body tomography, operated in a 3D acquisition mode, with a transverse resolution of 3.6–7.4 mm and an axial resolution of 4.0–6.7 mm. The images were reconstructed as 128 × 128 × 128 matrices of 2 mm × 2 mm × 2 mm pixels by means of filtered back-projection with a 0.5/cycles ramp filter (FWHM), followed by a 6-mm Gaussian filter resulting in an isotropic resolution of 7 mm.

Statistical Analysis

A comparison of respiratory/vascular variables and BIS scores between the baseline state and baseline + acupuncture were performed using Wilcoxon's matched pairs test. Results are represented as means ± SD.

The participants' tissue tracer activity images were computed into quantitative parametric rCBF images as described in a previous article (9).

RESULTS

All 13 volunteers were unconscious without eyelash reflexes 1.0 MAC sevoflurane, and none responded to needle insertion.

Cardiovascular Variables and BIS Values

Respiratory, vascular, and BIS values are presented in Table 1. The arterial partial pressure of carbon dioxide ($PAco_2$), mean arterial blood pressure, heart rate, and BIS values did not change significantly during acupuncture needle stimulation compared to baseline. No vasopressors were given.

Acupuncture-Associated Changes in rCBF During Needle Acupuncture

No significant change in global CBF was observed during needle acupuncture compared to baseline in the two groups (Table 1). Group I demonstrated a significant decrease in rCBF in the right medial frontal gyrus (20%) and in the left putamen (17%) when compared with baseline. Group II demonstrated a decrease in the right medial frontal gyrus (22%); in the putamen no significant changes were observed, both when compared with baseline.

DISCUSSION

This study revealed that acupuncture of LI-4 decreased rCBF in the contralateral putamen and in the ipsilateral medial frontal gyrus, whereas "placebo

acupuncture" only produced a decrease in the ipsilateral medial frontal gyrus. Therefore, these data suggest that needle penetration of the skin affects the medial frontal gyrus, while acupuncture of LI-4 influences the putamen.

Several studies have revealed modulation of rCBF in the putamen (among other results) during manual acupuncture of LI-4. (1,3,10) The putamen receives most of its input from the cerebral cortex, and in this sense, together with the caudate, it is a doorway into the basal ganglia. Experimental pain increases rCBF in the putamen and high levels of opioid receptors have been located at this site (11). Human studies suggest that dopamine may also play a role in central pain transmission and modulation, and that opioids influence dopaminergic transmission in the brain (12).

A number of cortical areas have been shown to be involved in pain processing. Frontal cortices are assigned the cognitive functions of organization and orientation of pain, and in one study, experimental pain was shown to cause activation of the ipsilateral medial frontal gyrus (13). According to our study, rCBF was decreased significantly in the medial frontal gyrus in both groups during needle insertion. Even during anesthesia needle penetration itself seemed to affect the brain, suggesting that the brain receives information of painful stimuli without conscious registration. However, it also seems to indicate a fundamental difference in how painful stimulus is interpreted while awake and during anesthesia, as Jones et al. (13) found an "activation," whereas we found a decrease in rCBF.

In recent years, there have been several imaging studies of cerebral activity during acupuncture analgesia. Wu et al. (14) concluded that the hypothalamus and limbic system modulate the effects of electroacupuncture as an analgesic in a fairly nonspecific manner. A very similar conclusion has been reached by other groups (1,3,5). Although many different neurotransmitters are used within the basal ganglia, the overall effect on the hypothalamus is inhibitory. Therefore, the observed decrease of rCBF in the putamen in the present study suggests that the key role of the hypothalamus in acupuncture-induced analgesia may be modulated via the putamen.

In the study set-up, the difference between false acupuncture and real acupuncture was limited to the needling point. Accordingly, the false acupuncture was expected to reveal the acupoint-specific response in the human brain, which we found to be deactivation of the putamen. In contrast the deactivation of the medial frontal gyrus was not significantly related to needle point. However, it should be noted that we are not aware of whether the selected points elicited "de Qi" sensation, as the volunteers were anesthetized. We had to rely on the well-known feeling of the "needle being grasped by a magnet." A recent study (15) has shown that the pattern of hemodynamic response to acupuncture of ST 36 (Stomach 36) depended on the psychophysical response to needle manipulation. When participants experienced "de Qi," the limbic and paralimbic structures, cerebellum, and brainstem demonstrated a concerted attenuation of signal intensity. When "de Qi" was mixed with sharp pain, the hemodynamic response was mixed, showing a predominance of signal increases instead (15). It is not yet clear how and if the anesthetic state of the brain affects its response to acupuncture. Although there are few publications related to this subject, the majority have demonstrated that acupuncture is also effective during anesthesia (16–18). The present study was performed to eliminate the influence of exogenous factors, such as expectation, fear, pain and environmental stimuli. For this reason, we conducted the study during anesthesia, which resulted in loss of consciousness.

Although the clinical relevance of this study may be limited, our results provide another foundation for future fMRI studies of the therapeutic effects of acupuncture. For the present, many questions remain unanswered due to the relatively limited work available on brain imaging and acupuncture.

We conclude that the putamen might characterize the central expression of acupuncture stimulation at the classical analgesic point LI-4 and serves as one key element in mediating analgesic efficacy.

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