Published in final edited form as:

Neurosci Lett. 2008 October 24; 444(2): 117–121. doi:10.1016/j.neulet.2008.08.033.

Electrical stimulation modulates the amphetamine-induced hemodynamic changes: an fMRI study to compare the effect of stimulating locations and frequencies on rats

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Abstract

Our previous fMRI and microdialysis measurements showed that electroacupuncture (EA) at LI4 was effective in alleviating excessive cerebral dopamine release induced by D-amphetamine (AMPH) in rats. We now compare the effect of EA in adjusting excess dopamine release at two stimulating frequencies (2Hz versus 100Hz at LI4) and at two acupoints (forepaw (LI4) versus hindpaw (ST36), at 2Hz). fMRI measurements of relative cerebral blood volume (rCBV) were used to monitor the brain activity of “rest”, followed by AMPH challenge, 10 minutes “rest”, and then 20 min of EA.

Results—EA at LI4 and ST36 significantly attenuated the AMPH-induced rCBV increases in the striatum, S1 cortex, and thalamus. Frequency: EA at 100Hz induced greater attenuation of rCBV than EA at EA at 2Hz in the S1, insula, anterior cingulate cortices, dorsolateral striatum, and thalamus. Acupoints: EA at LI4 modulated a broader area in the medial anterior striatum while EA at ST36 modulated a more site-specific area in the dorsolateral striatum. In the thalamus, EA at LI4 showed greater attenuating effect than EA at ST36 did. However, in the insular cortex, EA at ST36 showed stronger attenuation.

Conclusion—EA at both LI4 and ST36 was effective in restoring dopamine homeostasis from an excess state, with the most effective response at LI4 with 100Hz, while the responses to 2Hz EA at LI4 and ST36 showed slightly different spatial distribution of MR signal. This therefore provided insight into the neurophysiological basis of electroacupuncture effects in cortical and subcortical circuits.

Keywords

amphetamine; fMRI; rCBV; acupuncture; electroacupuncture; forepaw stimulation

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Introduction

Acupuncture is a popular alternative medicine with an estimated 8.2 million adults having ever used this treatment [2], for alleviating pain [11], nausea [27], and drug addiction [22, 28]. The overall effects of acupuncture are thought to be derived from physiological and psychological contributions [23]. Psychological factors such as emotion, expectation, or placebo effect, can easily be excluded from laboratory animals. The physiological contribution includes modulating activity in the peripheral [8], central [15, 35], and autonomic [10] nervous systems. Using a rodent model, we investigated the effects of electroacupuncture (EA) delivered using electrical paw stimulation (EPS) while measuring regional cerebral blood volume (rCBV) using functional magnetic resonance imaging (fMRI).

There is a large body of evidence indicating that electrical stimulation of the median nerve leads to modulation of dopaminergic function in normal controls and in Parkinson's patients [16, 29]. Using fMRI and microdialysis in rodents, we previously reported that EPS (2Hz) in the median nerve territory suppressed excessive dopamine (DA) release in the striatum--- a consequential result of enhanced glutamatergic and gamma-aminobutyric acid (GABA) activity [6]. There are multiple goals of the present study. The first goal is to investigate the frequency dependent effects of EPS using two clinically useful frequencies, 2Hz and 100Hz directed to the forepaw acupoint (LI4). Second, we test whether the dopamine modulating effect is specific to stimulation of the median nerve and therefore studied the effect of EPS on the forepaw (LI4) versus hindleg (ST36). Although clinical EA practice often uses stimulation with mixed frequencies (2–150Hz), certain conditions such as spasticity [12] use high frequency treatment while other conditions such as muscular atrophy [21] and arthritis [37] involve low frequency stimulation. In rodents, 100Hz EA suppresses the withdrawal syndrome of drug addiction [7, 34] while EA at 2Hz effectively suppresses craving in rodents addicted to heroin [32, 33]. Similar to our previous study [6], we used fMRI to assess relative cerebral volume (rCBV) changes in response to the degree of dopamine release. Massive DA release was induced by D-amphetamine (AMPH, a DA releaser) and EPS was initiated at the peak time of DA release (approximately 10 minutes after). Animals treated with AMPH alone (without EPS) served as our control to evaluate the effect of EPS in modulating the excessive DA release induced by AMPH.

Materials and methods

Animal preparation

All procedures were conducted in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 80-23) and of IACUC (Institutional Animal Care and Use Committee) approval through Massachusetts General Hospital. Male Sprague Dawley rats (200–300g) were anesthetized using 1% halothane in a mixture gas (1:1 O₂ and N₂O). A pair of 36 gauge acupuncture needles was inserted either at LI4 (Hegu) on the forepaw or at the ST36 (Zh Shan Li) on the hindleg. The two needles were secured in separated parallel partitions within a plastic tube and their tips were 1–2 mm apart. LI4 is located on the dorsum of the forepaw, approximately at the midpoint of the second metacarpal bone, in the belly of the first interosseus dorsalis muscle [20]. The location of LI4 is innervated superficially by the superficial branch of the radial nerve, and at its depth by the ulnar and median nerves. ST36 is located approximately 1 mm lateral to the tibial tuberosity, at the proximal one-fifth of the craniolateral surface of the leg distal to the head of the tibia in a depression between the muscles of the cranial tibia and the long digital extensor [20].

fMRI

Images were acquired repeatedly using a gradient echo EPI sequence with parameters published previously [6]. Spatial resolutions was 0.2345mm X 0.2345 mm X 1mm, and temporal resolution is 10s. Relative cerebral blood volume (rCBV) changes were assessed with MR contrast agent MION (synthesized in our laboratory) [5, 24]. Since the rCBV measurement is insensitive to the magnetic field strength [24], this study was carried out using 4.7T and 9.4T MRI scanners (Bruker, Billerica, MA). Ten baseline points were acquired before the injection of MION [5], followed by 30 post-MION baseline points, followed by an acute dose of AMPH (3mg/kg iv). Data was acquired continuously without interception from the pre MION baseline until 60 minutes after the administration of AMPH. EPS was applied 10 minutes after AMPH challenge for 20 minutes using “Han’s Acupoint Nerve Stimulator” (HANS, Model 202H). The electrical current oscillated at 2Hz (n=10 for LI4; n=12 for ST36 with images obtained from a 4.7T scanner) or 100Hz (n=14 for LI4 with images obtained from a 9.4T scanner). The initial current intensity was 1mA, with an increment of 0.2mA every 4 minutes with the highest current intensity to be 1.8mA.

Data analysis

Maps of rCBV responses were calculated on a pixel-by-pixel basis as described in [5, 24]. The rCBV time courses were drift corrected and characterized with two gamma functions using general linear model (GLM):

$$rCBV(t) = \Gamma_{\text{AMPH}}(t, t > 0) + \Gamma_{\text{EPS}}(t', t' > 10) = C_{\text{AMPH}} \cdot (t^* \exp(-t/\tau_{\text{AMPH}})) + C_{\text{EA}} \cdot (t'^* \exp(-(t'/\tau_{\text{EPS}})))$$

where Γ_{AMPH} characterizes the effect AMPH ($\tau_{\text{AMPH}} = 18$ min) and Γ_{EPS} characterizes the effect of EPS ($\tau_{\text{EPS}} = 15$ min), τ values were characterized from the previous study [6]. t' represents a delayed (10min) contribution of Γ_{EPS} to the total rCBV time course. C_{AMPH} and C_{EA} represent relative amplitudes for Γ_{AMPH} and Γ_{EPS} , respectively. The goodness of fit was presented by the statistical significance (p-values) on a pixel-by-pixel basis, and thus the maps of Γ_{AMPH} and Γ_{EPS} . Maps of Γ_{EPS} , C_{AMPH} , and C_{EA} were masked by map of Γ_{AMPH} map ($p < 10^{-4}$) to exclude rCBV changes that was not linked to AMPH activity. ROI analysis was performed on individual study and GLM analysis was performed on both individual and group level.

Results

Similar to the phenomenon we observed previously [6], EPS significantly attenuated the AMPH-induced rCBV increases and returned rCBV to baseline level at a rate faster than the natural pharmacological profile. In order to characterize the effect of EPS on the AMPH time courses, the rCBV responses were decomposed to the AMPH (Γ_{AMPH}) and EPS (Γ_{EPS}) components. The degree of attenuation from selected brain areas is shown in Figure 1 and in supplementary Figure S1. The maps of C_{AMPH} from the AMPH only (data from [6]), and the three groups which received EPS manipulation were highly similar to each other (supplementary Figure S2), indicating a reproducible brain response to AMPH challenge in all groups.

In general, EPS at LI4 and at ST36 significantly attenuated the AMPH-induced rCBV increases in many brain areas including the striatum, S1 cortex, thalamus, insular cortex (Figure 1). The detail differences between the stimulation locations (LI4 versus ST36) and frequencies (2Hz versus 100Hz) were further analyzed by subtracting the peak rCBV values of the Γ_{EPS} curves between the designated groups, pixel-by-pixel.

Frequency-specific response (at LI4)

The effect of 2Hz versus 100Hz stimulation at LI4 was evaluated by subtracting the peak rCBV values of two Γ_{EPS} maps (i.e., $C_{2\text{Hz}} - C_{100\text{Hz}}$). The results are shown in Figure 2. The degree of attenuation was greater by 100Hz than by 2Hz EPS in the S1, S2, insula, anterior cingulate cortices, dorsolateral striatum, and thalamus. Stimulation at 2Hz evoked greater inhibition in the medial striatum and in part of the cortex.

Acupoint-specific response (at 2Hz)

In general, at 2Hz, EPS at LI4 produced a stronger attenuation on the AMPH-induced rCBV increase than EPS at ST36. Similar to the frequency analysis, the effect of EPS at LI4 versus ST36 was evaluated by subtracting the peak rCBV values of the two C_{EPS} maps (Figure 3). EPS at LI4 induced a stronger and broader attenuation in S1 than EPS at ST36. In the striatum, EPS at LI4 modulated a broader area extending to the medial anterior part of striatum, while EPS at ST36 had a more intensive effect on the anterior-superior portion of striatum. In the thalamus, EPS at LI4 induced a stronger attenuation compared to ST 36. In contrast, the attenuation was stronger in the insular cortex at ST36 compared to LI4.

Discussion

We previously demonstrated that EPS significantly attenuated excessive synaptic dopamine and cerebral blood volume in the AMPH pretreated animals [6]. We hypothesized that the EPS modulating phenomenon is due to chain reactions initiated at the cortex, propagated to the striatum via glutamatergic projections, and subsequently enhanced GABA innervation to inhibit DA release [6]---a mechanism based on the circuit theory of the cortico-striato-thalamocortical (CSTC) loop. Using fMRI, we were able to track the temporal evolution of neuronal excitation elicited by AMPH (DA release and rCBV increases), and the subsequent neuronal inhibition elicited by EPS (DA release and rCBV suppression) throughout the entire rat brain. The current study revealed the effects of EPS at 2Hz and 100Hz at two stimulating locations and provides insight into the neural mechanisms that underpin acupuncture.

Compared with 2Hz, EPS at 100Hz led to a stronger CBV attenuation. This effect may be explained by the dynorphin/enkephaline-induced inhibition of dopamine release. Dynorphin, a kappa opioid receptor agonist, is known to decrease dopamine release and inhibit dopamine D1 receptor response in the striatum [31, 36]. Enkephaline, a mu/delta receptor agonist, also has a reciprocal effect on dopamine release [9]. Analysis of cerebral spinal fluid content showed that 2Hz EPS induced release of enkephalin while 100Hz EPS induced release of dynorphins [14] and the release of peptides was blocked by naloxone [14]. However, a higher dose of naloxone is required to block the effect induced by 100Hz stimulation, indicating a stronger neurochemical reaction induced by 100Hz stimulation. Thus, the stronger CBV attenuation exerted by EPS at 100Hz may be driven by the dynorphin-induced inhibition of dopamine release.

We also showed that the effects of EPS at 2Hz depend on the acupoint location. EPS at LI4 and ST36 both significantly attenuated the AMPH-induced rCBV increases. Detailed comparison showed that EPS at LI4 induced a stronger and broader attenuation in S1 than EPS at ST36 did. LI4 at the paw area has greater density of mechanoreceptors than ST36 around the knee [19] and the cortical presentation area is larger for the forepaw than knee. The relatively greater reduction in rCBV increase for LI4 stimulation may be related to the greater recruitment of local inhibitory networks encompassing a larger spatial territory in cortex. The striatum is known to receive topographically organized cortical afferents from functional and anatomical distinct areas and such topographic organization is maintained

through the CSTC loop [1, 25]. In rodents, the striatum contains a somatotopic body map consistent with cortical topography [3]. Retrograde stain and autoradiogram showed that the corticostriatal projection of hindpaw in the striatum is anterosuperior to that of forepaw [3, 4, 13]. In non-human primates, there is a dorsal to ventral shift of corticostriatal projection in the putamen in correspondent to the shift of dye injection sites from leg, arm, and to the face representation area in the somatic sensory and motor areas of the cortex [17, 18]. Our results showing that EPS at ST36 had a stronger effect than EPS at LI4 on the anterior-superior portion of striatum are consistent with histological evidence. The broader striatal reactivity induced by EPS at LI4 than at ST36 reflects the greater cortical representative volume for the forelimb than the hindleg, as shown in the S1 topographic study [19] and in the cortical CBV activity (Figure 2 and Figure 3).

The reason that EPS at ST36 had a stronger attenuation effect in the insular than EPS at LI4 is unclear. fMRI studies showed that emotionally relevant context for sensory experience [30] and acupuncture stimulation [26] induced hemodynamic (BOLD signal) increases in the insular in humans. The insular cortex is reciprocally connected with the secondary primary sensory cortex (SII) and receives thalamic input. The stronger counter effect generated by EPS at LI4 thus led to a weaker attenuation effect in the AMPH-induced rCBV increases.

The present study has demonstrated frequency and location-specific effects of EPS, a stimulus that closely parallels electroacupuncture and is commonly used in human clinical settings. One caveat is that this set of data was obtained from anesthetized rats. Whether or not the use of anesthetic would yield results different from those obtained from awake animals remains to be studied. Nonetheless, our data suggest that specific loci within the CSTC loop are differentially altered by the stimulus parameters of EPS. Though questions regarding the pathological basis of EA in humans remain, the rodent model has revealed that the mechanism likely involves a suppression of DA systems in response to stimulation of the CSTC circuit. The magnitude of DA suppression depends on both the frequency and location of electrical acupuncture.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding agency: sponsored by NIH/NCCAM grant PO1 AT002048

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Figure 1.

The goodness of fit for Γ_{EPS} , shown as maps of p-values. EPS at LI4 (both 2Hz and 100Hz) and ST36 (2Hz) significantly attenuated the AMPH-induced rCBV changes.

Figure 2.

Inter-group comparison of Γ_{EPS} for the attenuation effect of EPS between 2Hz and 100Hz at LI4. (A) Difference map of the peak rCBV values of the $\Gamma_{2\text{Hz}}$ and $\Gamma_{100\text{Hz}}$ at LI4, i.e. $C_{2\text{Hz}} - C_{100\text{Hz}}$. (B) rCBV time courses from the cingulate cortex (only pixels with $p < 10^{-4}$ in Γ_{EA} fitting was included). Both 2Hz and 100Hz fit to a same Γ_{AMPH} function (green solid line), while the amplitude of $\Gamma_{100\text{Hz}}$ (blue solid line) is bigger than that of $\Gamma_{2\text{Hz}}$ (red solid line), indicating a stronger attenuation effect by 100Hz.

Figure 3.

Inter-group comparison of Γ_{EPS} for the effect of EPS between LI4 and ST36 at 2Hz. (A) Difference map of the peak rCBV values between Γ_{ST36} (blue solid line) and Γ_{LI4} (red solid line) at LI4, i.e. $C_{ST36} - C_{LI4}$. rCBV timecourses from the insulate cortex (B) and S1 cortex (C). The EPS induced attenuation was stronger at ST36 in the insulate cortex but weaker in the S1 cortex than the effect produced at LI4. Note that the apparent “increase” of the rCBV response in the ST36 group between $t=40-80$ min actually reflects a fast declining rate of Γ_{ST36} relative to a slower declining rate of Γ_{AMPH} . During this period of time, rCBV is back to the level of Γ_{AMPH} that remains at an elevated level.