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*Original Article*

# The change in cerebral glucose metabolism after electroacupuncture: a possible marker to predict the therapeutic effect of deep brain stimulation for refractory anorexia nervosa

Tao-Tao Liu[1], Qing-Xiong Hong[2], Hong-Bing Xiang[1]

[1]*Department of Anesthesiology and Pain Medicine, Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei, PR China;* [2]*Department of Anesthesiology, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou 510120, PR China*

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**Abstract:** Some reports have demonstrated that deep brain stimulation (DBS) is a promising treatment for patients who suffer from intractable anorexia nervosa. However, the nature of DBS may not be viewed as a standard clinical treatment option for anorexia nervosa because of the unpredictable outcome before DBS. Just like DBS in the brain, electroacupuncture at acupoints is also efficient in treating refractory anorexia nervosa. Some neuroimaging studies using functional magnetic resonance imaging, single-photon emission computed tomography (SPECT), and positron emission tomography (PET) had revealed that both DBS and electroacupuncture at acupoints with electrical stimulation are related to the changes in cerebral glucose metabolism. Therefore, we hypothesize that the changes in cerebral glucose metabolism after electroacupuncture might be useful to predict the therapeutic effect of deep brain stimulation for refractory anorexia nervosa.

**Keywords:** Cerebral glucose metabolism, electroacupuncture, deep brain stimulation, anorexia nervosa

## Introduction

Anorexia nervosa is a complex and chronic course that is refractory to standard clinical treatment in many patients and has one of the highest relapse rates of any psychiatric disorder [1]. It's well known that deep brain stimulation (DBS) is a type of non-resective, adjustable, and reversible therapy. Preliminary results from human clinical trials showed that the use of DBS to treat anorexia nervosa may be a valuable option for weight restoration in otherwise-refractory and life-threatening cases [1-6]. It has been reported that the therapeutic mechanisms of DBS for treatment-refractory anorexia nervosa and epilepsy may be related to the changes in cerebral glucose metabolism [5, 7]. Otherwise, a randomized cross-over pilot study showed potential of the benefit of acupuncture as an adjunct therapy in the treatment of anorexia nervosa and bulimia nervosa particularly in the area of quality of life [8, 9]. Changes of glucose metabolism in specific brain areas following stimulation by acupuncture on LR3 and ST44 were documented using fluorodeoxyglucose positron emission tomography (FDG-PET) combined computed tomography (CT) [10]. Needling at TE5 had a regulating effect on cerebral functional areas shown by PET-CT, and this may relate to its impact on the recovery of post-stroke patients [11]. Recent studies have demonstrated that needling in Baihui, Shuigou and Shenmen enhances glucose metabolism in the frontal lobes, thalamus, temporal lobe, and the lentiform nucleus in vascular dementia [12]. Some neuroimaging studies using functional magnetic resonance imaging, single-photon emission computed tomography (SPECT) had revealed that glucose metabolism significantly increased in the frontal gyrus following electroacupuncture at Hegu (LI 4) and Quchi (LI 11) [13, 14]. Therefore, the clinical effect of electroacupuncture at acupoints for anorexia nervosa and vascular dementia is also related to

the changes in cerebral glucose metabolism. And it has been presumed that the cerebral changes after electroacupuncture at acupoints could predict the efficacy of deep brain stimulation in pharmacoresistant anorexia nervosa patients because both deep brain stimulation and electroacupuncture at acupoints are related to the changes in cerebral glucose metabolism.

## The hypothesis

Studies in rodents and humans have highlighted that both deep brain stimulation and electroacupuncture at acupoints are effective in treating medically refractory anorexia nervosa, and more importantly, are both related to the change in cerebral glucose metabolism [14-29]. Therefore, we hypothesize that that the change in cerebral glucose metabolism after electroacupuncture may be a marker of predicting the therapeutic effect of deep brain stimulation for refractory anorexia nervosa.

## Evaluation of the hypothesis

*The therapeutic mechanism of DBS for medically refractory anorexia nervosa is related to the changes in cerebral glucose metabolism*

Several lines of evidence have indicated that the therapeutic mechanism of DBS for circuit-based neuropsychiatric diseases (such as refractory epilepsy, Parkinson's disease, major depression, and medically refractory anorexia nervosa) is related to the changes in cerebral glucose metabolism. Lipsman et al reported the use of subcallosal cingulate DBS for the treatment of people with severe and enduring anorexia nervosa, and showed improvements in their physical status-benefits that seemed to be mediated by improvements in mood and anxiety rather than caused by a direct effect on appetite; With respect to the PET scan results, the voxel-wise analyses of the standardised-uptake-value data revealed that glucose metabolism was increased in posterior cortical regions, the right middle and right inferior temporal gyrus, left post-central gyrus, right precuneus, right supramarginal gyrus, right inferior parietal lobule, and left cuneus [5]. Otherwise, Batisse-Lignier et al [30] studied the changes in regional glucose metabolism following STN-DBS-treated patients with PD, and showed that endogenous glucose production (EGP) and whole-body glucose disposal rates (GDRs) were higher in PD patients in Stim-OFF conditions than in the control group by assessing in the postabsorptive state. By employing [(18) F] fluorodeoxyglucose (FDG) positron emission tomography (PET) study, Nagaoka et al [31] also found that STN-DBS increased the regional cerebral metabolic rate of glucose (rCMRGlc) in the posterior part of the right middle frontal gyrus, which corresponded to the premotor area, and the right anterior lobe of the cerebellum. These findings indicated that DBS-induced metabolic changes are tightly linked to glucose metabolism in CNS.

*The therapeutic mechanism of electroacupuncture at acupoints is tightly linked to the changes in cerebral glucose metabolism*

Cerebral functional imaging has been successfully combined with acupuncture researches. Accumulating evidence has shown that clinical effect of electroacupuncture at acupoints is also tightly linked to the changes in cerebral glucose metabolism. It has been reported using PET that the glucose metabolism changed significantly on primary motor area (M1), premotor cortex (PMC), and superior parietal louble (LPs) bilaterally, as well as the supplementary Motor Area (SMA) on the unaffected hemisphere right after the first EA treatment in 6 patients suffering from ischemic stroke after receiving EA treatment at Baihui (GV20) and right Qubin (GB7) [32]. Huang et al showed that needling at Waiguan (TE5) could improve the glucose metabolism of the healthy hemisphere while decreasing the glucose metabolism of the affected hemisphere, and this might be the mechanism underlying the role of acupuncture in the recovery of hemiplegia [11]. These findings indicated an implication of cerebral glucose metabolism in the effect of electroacupuncture at acupoints.

*The central melanocortin system regulates glucose metabolism*

The central nervous system (CNS) melanocortin pathway plays an important role in regulating appetite, body weight homeostasis and energy expenditure [33], and these effects are mediated mainly via activation of G protein-coupled melanocortin-4 receptors (MC4R) expressed in the brain, which is central to the

control of food intake [34]. A number of studies have verified that MC4R in the central nervous system are key regulators of and glucose metabolism, and have also been suggested to regulate the release of insulin via the activity of sympathetic neurons [35]. Recently, by using MC4R-green fluorescent protein (GFP) transgenic mouse model, our group demonstrated that neurons expressing MC4R-GFP were distributed in anterior cingulate, insula, parietal lobe and middle frontal gyrus, which were in line with a previous immunohistochemical study showing that the anterior cingulate, insula, parietal lobe, primary motor area (M1), premotor cortex (PMC), and frontal gyrus exhibited moderate levels of GFP immunoreactivity using a mouse line in which GFP is expressed under control of MC4R gene promoter [36], suggesting that MC4R signaling in the anterior cingulate, insula, parietal lobe, and frontal gyrus may involve the melanocortinergic regulation of glucose metabolism.

## Conclusions

In conclusion, DBS and EA at acupoints are both related to the changes in cerebral glucose metabolism. By analyzing changes of glucose metabolism in corresponding CNS nucleus with inexpensive and mini-invasive approaches, we probably could predict the response of patients with refractory anorexia nervosa after applying EA at acupoints. Certainly, future studies are required to approve this hypothesis.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Qing-Xiong Hong, Department of Anesthesiology, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou 510120, PR China. E-mail: hqx1095@163.com

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