

Research progress of the central mechanism of acupuncture-moxibustion for simple obesity

针灸治疗单纯性肥胖的中枢机理研究进展

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Abstract

Obesity often results when regular caloric intake exceeds the energy expenditure. Hypothalamus is the center that regulates feeding and energy balance inside the body, especially the lateral hypothalamic area (LHA) and ventromedial nucleus (VMN). Acupuncture-moxibustion has achieved significant progress in treating simple obesity, and the relevant studies have revealed the central action mechanism underlying the treatment. By reviewing the literatures associated with the mechanism studies on acupuncture-moxibustion for simple obesity, this article is going to provide clinical and scientific guidance for the treatment of simple obesity with acupuncture-moxibustion.

Keywords: Acupuncture Therapy; Moxibustion Therapy; Acupuncture-moxibustion Therapy; Obesity; Hypothalamus

【摘要】肥胖产生的根本原因是能量摄入超过能量消耗的正平衡。下丘脑是调节摄食活动和体内能量平衡的中枢，下丘脑外侧区(LHA)和腹内侧核(VMN)与机体的进食密切相关。针灸治疗单纯性肥胖取得了重大进展，针灸治疗单纯性肥胖的基础研究揭示了针灸治疗单纯性肥胖的中枢相关机制。通过综述近年来针灸治疗单纯性肥胖的中枢机理研究文献，为针灸治疗单纯性肥胖的临床和科研提供指导。

【关键词】针刺疗法；灸法；针灸疗法；肥胖；下丘脑

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Obesity is a medical condition in which excessive body fat has accumulated due to calories taken more than needed. There are simple obesity and secondary obesity, and the former is most commonly seen, occupying around 95% of the obesity people^[1]. In the 21st century, obesity has become a health threat worldwide, and it's become an urgent job to prevent and treat obesity. As the current weight loss medications may cause side effects, along with drug tolerance and high relapse rate, it's of great significance to seek an effective treatment for obesity. As a green therapy, acupuncture-moxibustion is effective and free of adverse effects in treating obesity. During the recent years, great progress has been achieved in studying the central mechanism underlying the treatment of simple obesity with acupuncture-moxibustion.

For studying the central mechanism, we conducted computer retrieval and analyzed the collected literatures.

The retrieved databases and time range: Ovid-MEDLINE (1946-2016.6); Excerpta Medica Database (EMBASE, 1974-2016.6); Ovid-BIOSIS Previews (1980-

2016.6); Chinese Journal Full-text Database (CJFD, 1980-2016.6); Chinese Biomedical Literature Database (CBM), Chongqing VIP (VIP) and Wanfang Academic Journal Full-text Database (Wanfang) (from founding of the databases to 2016.6).

Retrieval method: Without limitation of languages. The key terms were acupuncture therapy, moxibustion, acupuncture-moxibustion, obesity, hypothalamus, and central mechanism. The retrieval strategy was generated by the librarian, who had over ten years of work experience, together with the study group. The collected literatures are reviewed as follows.

1 Causes of Simple Obesity

Basically, obesity occurs when the body takes in more calories than needed and excessive body fat has accumulated, pathophysiologically featured by metabolic dysfunction of fat tissues (accelerated synthesis and inhibited decomposition) which leads to excessive accumulation of body fat. It's found that in the central nervous system, the hypothalamus regulates feeding and energy balance, and the central nervous dysfunction may lead to bulimia, consequently causing obesity^[2]. Via stimulating acupoints and modulating the function of the meridians and Zang-fu organs,

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acupuncture-moxibustion helps to lose weight. A laboratory study found that acupuncture can significantly improve the morphological structure of obesity rats. By using optical or electron microscopes, some scholars observed the fat tissues, small intestinal mucosa and liver structure of obesity rats, as well as the morphological changes after acupuncture^[3]. The results showed that brown stained lipocytes were enlarged, lipid droplets were enlarged, cytoplasmic mitochondria decreased, intercellular spaces became narrower, and capillaries were reduced; after acupuncture, the above morphological alterations were all reversed, which provided direct morphological evidence to prove the weight losing effect of acupuncture. During the recent years, most of the studies on the central mechanism of acupuncture in treating obesity were focused on hypothalamus, since it's closely associated with feeding and the initial cause of obesity is the out-of-control food intake. So, what's the regulation relationship between the hypothalamus and food intake?

2 Basic Research on Hypothalamus

The hypothalamus mainly consists of medial and lateral areas. The medial nuclei majorly include arcuate nucleus (ARC), ventromedial nucleus (VMN), dorsomedial nucleus (DMN), paraventricular nucleus (PVN), suprachiasmatic nucleus (SCN), and perifornical nucleus (PFA); the lateral area, named lateral hypothalamic area (LHA), has a centralized function and a neuroanatomical structure. Previous research has proved: the hypothalamus contains two sections in control of food intake, of which, LHA is called hunger center and VMN satiety center. When the hunger center is stimulated, the food intake will significantly increase; when the satiety center is stimulated, animals will immediately stop taking food^[4]. Further studies also revealed that ARC, DMN, PVN, SCN nuclei have a complicated synaptic connection with VMN and LHA. These nuclei are composed of various neurotransmitters, neurons, neuropeptides, relative genes, and action targets of a variety of neural signals, forming up a network for regulating food intake. Binding to neuroactive substances will lead to various activities of hypothalamic nuclei to regulate food intake and energy metabolism via this network.

Therefore, we hypothesize that the action of acupuncture in treating obesity should be a regulatory action on the network in charge of food intake. The weight losing effect of acupuncture should be produced by working on multiple brain sections, neurons, neural information, and the involved genes. So, here comes a question: what are the central mechanisms underlying acupuncture in treating obesity?

3 Possible Central Mechanism of Acupuncture-moxibustion in Treating Simple Obesity

3.1 Regulatory effect on the center

It's found that the regulation of feeding and energy metabolism from the central nervous system involves a network made up by multiple nuclei and neurons. Hence, the disorders of the central nervous system in an obesity body also involve multiple brain areas, nuclei, neurotransmitters, neuropeptides, active enzymes, and genes^[5].

3.1.1 Regulatory effect on the discharge of neurons

By adopting electrophysiological and stereotaxic techniques, Zhao M, *et al*^[6] observed the electrical activity of neural cells in LHA and VMN of obesity rats before and after acupuncture. The results showed that acupuncture down-regulated the excitability of LHA and up-regulated the excitability of VMN, suggesting that acupuncture should achieve a negative energy balance and reduce body weight by inhibiting the appetite of obesity rats and reducing the intake of calories. Liu ZC, *et al*^[7-8] also observed the influence of acupuncture on the spontaneous discharge of the neural cells in VMN and ARC of obesity rats. It's unveiled that acupuncture should promote the excitability of the neural cells by increasing the spontaneous discharge frequency. These studies all indicated that acupuncture can produce a bilateral benign regulation on the discharge of neural cells in LHA, VMN and ARC, the areas responsible for modulating food intake, which should be one of the mechanisms underlying the weight losing effect of acupuncture.

3.1.2 Regulating the hypothalamic areas in charge of feeding

Huang XY^[9] and Xia SY^[10] examined the hypothalamic feeding center and its relative nuclei before and after electroacupuncture (EA) at the right Zusanli (ST 36) and Neiting (ST 44) by functional magnetic resonance imaging (fMRI). It's showed that after EA, LHA presented functional inhibition, which lasted even after the EA intervention, indicating that EA at Zusanli (ST 36) and Neiting (ST 44) can restrain the hyperactive appetite and ease the hunger sensation, which should be a key point in the treatment of obesity with acupuncture. Luo XJ^[11] observed the effect of acupuncture-moxibustion on the central nervous center of obesity adolescents via fMRI. Compared to the pre-intervention state, when stimulated by pictures of food, the activities of bilateral orbitofrontal cortex, insular cortex, posterior cingulate cortex, occipital lobe, and left cerebellum were inhibited after acupuncture-moxibustion. It's supposed that acupuncture can not only produce a short-term effect on central nervous system in treating obesity, but also can lead to the rebuilding of cortex. By using an obesity

rat model and neuroimaging techniques, further studies explored the central pathogenesis of obesity and the action mechanism of acupuncture-moxibustion in losing weight, and discovered the differences between obesity rats and normal weight rats in comparing the dysfunction of the involved areas. The static fMRI results showed activated bilateral hippocampus and right thalamus and hypoactivated occipital lobe. Acupuncture-moxibustion enhanced the activities of bilateral olfactory bulbs, frontal cortex, right insular cortex, and hippocampus, and inhibited the activities of right thalamus. Therefore, it's held that the development of obesity should be associated with the dysfunction of central nervous system, anatomical and physiological foundations^[11].

3.2 Modulating neurotransmitters

Currently, the action mechanism of acupuncture-moxibustion in modulating neurotransmitters has been profoundly studied, majorly from the perspectives of catecholamines, 5-hydroxytryptamine (5-HT), cholecystokinin (CCK), vasoactive intestinal peptide (VIP), neuropeptides and leptin (LP).

3.2.1 Catecholamines and 5-HT

Catecholamins [noradrenaline (NA), adrenaline (Adr), and dopamine (DA)] and 5-HT are important monoamine neurotransmitters in regulating the feeding center. The two types of substances influence the feeding center via mutual restriction^[12]. Han Y, *et al*^[13] studied the effect of acupuncture on obesity rats, and found that acupuncture can correct the abnormal ratio between catecholamine and 5-HT and restore the function of hypothalamic feeding center. Wei LQ observed the influence of acupuncture on the monoamine transmitters in brainstem raphe nuclei of obesity rats^[14]. The results showed that the contents of 5-HT and 5-HT/5-hydroxyindole acetic acid (5-HIAA) in brainstem raphe nuclei increased, and the metabolism rate also rose up, suggesting that acupuncture should achieve its weight losing effect by influencing the function of VMN and reducing the intake of calories. The study conducted by Su J, *et al*^[15] proved that acupuncture can produce a benign regulatory effect on the abnormal neurotransmitters in hypothalamic VMN and amygdala of obesity rats. Liu ZC, *et al*^[7] observed the effect of acupuncture on the monoamine neurotransmitters in hypothalamic VMN of obesity rats. The study found that acupuncture up-regulated the level of tyrosine (Tyr), DA, tryptophan (Trp), and 5-HT/5-HIAA in VMN, indicating that the benign regulation effect on VMN should be a key factor underlying acupuncture in treating obesity. Liu ZC, *et al*^[16-17] also observed the effect of acupuncture on the monoamine neurotransmitters in obesity rat's striatum and amygdala. It's found that acupuncture up-regulated the level of Tyr, DA, NA, Trp, Ca²⁺-ATP (adenosine triphosphate), and down-regulated the level

of 5-HT and 5-HT/5-HIAA, suggesting that the regulation effect on striatum and amygdala should be one of the central mechanisms of acupuncture in the treatment of obesity. The same study group^[18] investigated the monoamine neurotransmitters and ATPase activity in LHA of obesity rats, and found that acupuncture down-regulated the NA content, up-regulated the level of 5-HT, and the activities of Mg²⁺-ATPase and Ca²⁺-ATPase in LHA. Liu ZC, *et al*^[19] also observed the effect of acupuncture on the level of nitric monoxide (NO) and NO synthetase (NOS) in hippocampus of obesity rats. It's showed that the content of NO and activity of NOS in hippocampus descended after acupuncture. Therefore, it's believed that the regulation effect on the content of NO and activity of NOS in hippocampus should be one of the central mechanisms of acupuncture in exerting the weight losing effect. A study performed by Liu ZC, *et al*^[20] investigated the influence of acupuncture on the monoamine neurotransmitters in raphe nuclei of obesity rats. It's found that acupuncture up-regulated the content of 5-HT and down-regulated DA content in raphe nuclei, indicating that acupuncture can produce a benign regulation effect on monoamine neurotransmitters in raphe nuclei. The above studies all suggested that acupuncture can produce a benign regulation effect on the abnormal monoamine neurotransmitters in central nuclei, which is possibly one of the mechanisms of acupuncture in treating obesity.

3.2.2 CCK and VIP

CCK, a type of important monoamine neurotransmitter, is widely distributed in central nervous system and involved in the regulation of gastrointestinal and biliary tract motilities. VIP takes part in the regulation of the function of multiple systems. Liu ZC, *et al*^[21] observed the content of cortical CCK and VIP in obesity rats before and after acupuncture, and found the content of CCK and VIP was extremely low in obesity rats but increased after acupuncture. Hence, it's held that the benign regulation acupuncture produced on CCK and VIP contents should be an important mechanism in treating obesity.

3.2.3 Neuropeptide Y (NPY) and LP

NPY (a crucial appetite-stimulating factor, can enhance appetite and food intake) and LP are two important appetite-regulating factors. They are both apposite and complementary to each other, playing an important role in the development of obesity. LP inhibits the expression and promotes the decomposition of NPY, finally lowering the content of NYP^[22]. LP not only restrains food intake, but also increases energy consumption, majorly through working on hypothalamic LP-receptor and up-regulating the production of peripheral NA, which can activate β 3-adrenergic receptor (β 3-AR) on lipocytes and release the heat transformed from energy^[23]. Sun Z, *et al*^[24-25]

found that the expression of NPY mRNA in hypothalamic ARC dropped significantly after acupuncture in obesity rat models, while the expression of LP-receptor gene, obese gene receptor (OB-R) mRNA increased significantly. It's suggested that acupuncture can regulate the synthesis and secretion of NPY via increasing the expression of OB-R mRNA and inhibiting the expression of NPY mRNA, which should be an important action mechanism underlying the weight losing effect of acupuncture. By adopting a food-induced obesity rat model, Liu X, *et al*^[26] discovered that the body weight (BW), insulin resistance index, agouti gene-related protein (AGRP) in hypothalamus, NPY, and diameter of lipocytes in the EA and Western medication groups were significantly lower than that in the obesity model group ($P < 0.05$), thus holding that EA can inhibit the expression of NPY and AGRP via improving insulin resistance, and finally realize BW control. Liu X, *et al*^[27] further explored the action mechanism of EA in losing weight by focusing on the effect of EA on body weight (BW), insulin resistance, and hypothalamic insulin signaling molecules. The results showed that EA can improve insulin resistance, inhibit the increase of BW, and improve the fatty degeneration of liver via lowering the expression of phosphoinositide 3-kinase p85 subunit (PI3K-p85), which should be one of the action mechanisms of EA in producing its weight losing effect. Qu YT, *et al*^[28] studied the influence of EA on the BW, morphological change of lipocytes, insulin resistance, protein tyrosine phosphatase-1B (PTP-1B) and insulin receptor substrate-1 (IRS-1) in hypothalamus of food-induced simple obesity rats, for exploring the action mechanism of EA in treating obesity. It's found that EA can improve the insulin resistance, inhibit the increase of BW, and improve the size of lipocytes via down-regulating the expression of PTP-1B protein, which should be another crucial mechanism behind the weight losing effect of EA.

4 Conclusion and Prospect

Nowadays, acupuncture-moxibustion has become a valuable option in the treatment of simple obesity. The weight losing effect that acupuncture-moxibustion produces is closely associated with its regulation on hypothalamic function. The experimental studies have proven that this weight losing effect should be an integrated action involving multiple brain areas, nuclei, neurons and information substances^[29]. It's also found that acupuncture can produce a benign regulation on various brain areas, nuclei, neurotransmitters, neuropeptides, hormones and receptors, and consequently correct the dysfunction of nerves, endocrine and metabolism, inhibit the intake of calories and increase the energy consumption, and finally achieve the goal of losing weight^[30]. Studies on central

mechanisms of acupuncture-moxibustion in losing weight are majorly focused on nerves, electrophysiology, and content of neurotransmitters, and preliminarily involve the expression of several genes^[31]. Up till now, the central mechanism of acupuncture-moxibustion in treating obesity mainly covers three aspects: regulation of the discharge of central neurons; regulation of hypothalamic feeding center; regulation of central monoamine transmitters. Generally speaking, acupuncture-moxibustion has a bright future in the treatment of simple obesity. But, its treatment mechanism hasn't been fully elucidated. Therefore, based on the previous achievements, molecular biological techniques should be introduced into future studies, for further revealing the effect of acupuncture-moxibustion on NPY and its gene expression, as well the uncoupling protein and its gene expression^[31]. In the future, more and more obesity-related factors will be discovered, and their mutual actions will be clearer, benefiting the understanding of the neural network dysfunction in obesity^[32]. Meanwhile, the action mechanism of acupuncture-moxibustion in treating obesity will also be more crystal.

Conflict of Interest

The authors declared that there was no potential conflict of interest in this article.

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