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OVERVIEW

Electroacupuncture in the Treatment of Obesity

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Abstract Obesity is becoming one of the most common health problems in the world. Many other disorders, such as hypertension and diabetes are considered as the consequences of obesity. Since effective remedies are rare (only two drugs, Orlistat and Sibutramine, were officially approved by the US Food and Drug Administration for long-term obesity treatment so far), researchers are trying to discover new therapies for obesity, and acupuncture is among the most popular alternative approaches. To facilitate weight reduction, one can use manual acupuncture, electroacupuncture (EA) or transcutaneous electrical acupoint stimulation (TEAS). As the parameters of the EA or TEAS can be precisely characterized and the results are more or less reproducible, this review will focus on EA as a treatment modality for obesity. Results obtained in this laboratory in recent five years will be summarized in some detail.

Keywords Electroacupuncture · Obesity

Effect of Electroacupuncture (EA) on Weight Loss

In the literature, most of the reports indicated that both body acupuncture and auricular acupuncture were effective for weight reduction in obese subjects [1–3], although some negative reports also existed [4, 5]. An attempt was made to clarify whether electroacupuncture (EA) of strictly identified parameters is effective to suppress the simple obesity induced by high energy diet in a rat model. In the diet-induced obese (DIO) rats, EA was applied at the hind leg acupoints ST36 (adjacent to the knee joint) and SP6 (adjacent to the ankle joint) three times per week for 4 weeks with high energy diet and water provided ad libitum. A significant reduction of the body weight accompanied by a reduction in food intake was observed. 2 Hz EA was more effective than 100 Hz EA [6]. Theoretically, this reduction may be accounted for by a decrease in food consumption, an increase in energy expenditure or a combination of both. In the following we chose to use 2 Hz EA to further analyze the underlying mechanisms.

EA Caused a Suppression of Appetite

There have been reports of reduced appetite or craving for food from subjects wearing auricular acupuncture devices [1, 7, 8]. The conclusion was usually obtained according to subjective reports rather than quantitative analysis of the food intake. In our animal study, we measured daily food intake of the rats, and found a reduction of food consumption in the EA treatment group compared to control group subject to restraint only ($P < 0.001$). This reduction was positively correlated with weight loss. It was noticeable that when rats were administered with 2 Hz EA every other day, a reduction of food consumption was observed only on the day of EA administration, suggesting that the effect of EA on appetite suppression lasted for <24 h. Considering the fact that most of the food consumption occurred in the dark phase, we compared the effect of EA treatment delivered in the dark versus light. 2 Hz EA

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delivered just before the dark phase was more effective than that at the end of the dark phase, suggesting once again that the effect of EA in reducing food intake was immediate and short lasting (unpublished data).

To see whether the effect of EA is due to its stressful and depressive reaction, open-field task and sugar water consumption test were performed. Comparing with the control rats, sugar water consumption and crossing scores in the EA group were not decreased, even with an increase of rearing score, implying that the reduction of food intake was not resulted from EA-induced stress and/or depression [9]. In fact, acupuncture and EA have been reported to treat clinical depression with considerable success [10, 11].

Possible Mechanisms Underlying the Appetite Suppressive Effect of EA

The arcuate nucleus of hypothalamus (ARH) is a crucial integrative center for modulation of food intake [12, 13]. The ARH contains at least two populations of neurons that have opposite influence on food intake. One population expresses the anorexigenic peptide "alpha-melanocyte-stimulating hormone" (α-MSH; derived from the precursor proopiomelanocortin or POMC). The other population expresses the orexigenic peptide "neuropeptide Y (NPY)". Neurons in the ARH subsequently innervate various second order hypothalamic targets that express melanocortin- and NPY-receptors [14]. Our previous study indicated that 2 Hz EA-induced c-fos expression in ARH, which implied that 2 Hz EA might exert a regulatory effect on gene expression in this nucleus [15]. It was demonstrated that in obese rats with hyperphagia, the expression of POMC in ARH was significantly decreased [16, 17]. 2 Hz EA treatment produced an increase in the expression of mRNA encoding POMC as well as an increase of the peptide level of α-MSH [18], without affecting NPY level [9]. The later may have been accounted for by the fact that the peptide level of NPY was already very low in obese rats [9, 16].

In order to have a close look at the effect of EA on the expression of NPY, we put the rat in a food restriction (FR) status, i.e., food was allowed only for 1 hour per day. In this case, the expression of NPY in the ARH was significantly increased as compared to ad lib-fed rats. In this extreme case, 2 Hz EA treatment produced a further decrease of food intake accompanied by a further reduction of the body weight. In the meantime, there was a down-regulation of NPY expression [19].

Thus, an increase of α-MSH expression and a reduction of NPY expression in the hypothalamic arcuate nuclei may constitute at least part of the mechanisms underlying the effect of 2 Hz EA for decrease of appetite and reduction of body weight.

Shiraishi et al. [20] reported that auricular acupuncture applied to rats produced a reduction of the neural activity of lateral hypothalamus (LH, considered as the "feeding center") and an increase of the neural activity of ventral medial hypothalamus (VMH, considered as the "satiety center"). Zhao et al. [21] applied EA at Zusanli (ST36) and Neiting (ST44) of the rat and observed that EA produced an increase in the electric activity of VMH in the obese rat, suggesting an activation of the satiety center. Since VMH and LH are functionally down stream of ARH, neuron-peptides released from ARH might take part in the control of the neural activity in LH and VMH in mediating EA effect.

Recently, cocaine- and amphetamine-regulated transcript (CART) was found coexisting with α-MSH in ARH to suppress appetite [22]. We found that EA stimulation increased the peptide level of CART in ARH [6], which implied that EA might regulate a cohort of peptides in ARH to negatively modulate food intake and energy balance. Genomic and proteomic analysis may help to clarify the EA-induced changes in the profile of gene expression and protein expression in the ARH.

EA Does Not Affect Energy Expenditure via AMPK–UCP3 Pathway

It is well known that the basal metabolic rate (BMR) is higher in obese subjects or rodents compared with their lean controls [23–25]. It remained to be explored whether acupuncture could further increase BMR in obese state. This aspect was neglected by most of the studies on acupuncture in this field. It has been shown that uncoupling protein 3(UCP3) in the muscle accelerates the utilization of fatty acids as energy substrate and UCP3 mRNA expression is positively associated with energy expenditure [26]. Several studies had implied that UCP3 may serve as a new target in reducing body weight by up-regulating energy expenditure [27–30]. We wanted to explore whether EA treatment increased UCP3 protein level in the muscle of obese rats. No significant change in the content of UCP3 protein was observed after 2 Hz EA treatment. It has been shown that the 5′-AMP-activated protein kinase (AMPK) is a potent regulator of skeletal muscle metabolism [31]. The expression of UCP3 could be up-regulated by the activation of AMPK [32], and a deletion of AMPKα resulted in a decrease of UCP3 expression in muscle [33]. In consistent with the observation of UCP3, neither phosphorylated nor total protein level of AMPKα were changed by 2 Hz EA treatment. Therefore, the effects of 2 Hz EA in reducing body weight seem to be a result of decrease of food intake rather than an increase of energy expenditure through AMPK–UCP3 pathway.

Effects of EA in Circulating Metabolites

Liu et al. [34] applied ear- and body-acupuncture to obese subjects, and found a decrease in plasma levels of triglyceride, total cholesterol and LDL cholesterol as well as an increase in the HDL level. Similar findings were reported by Sun and Xu [35]. Since the manipulation of the needle according to traditional Chinese medicine is difficult to characterize, we took advantage of using precisely identified frequency and intensity of the electrical stimulation applied on needles inserted into the acupoints. As was reported before, diet-induced obese rats showed an increased level of plasma cholesterol and triglyceride, but the plasma glucose content remained at the same level of the lean rats. Neither 2 Hz- nor 100 Hz EA changed plasma glucose level. EA produced a reduction of plasma level of total cholesterol and triglyceride. In this respect, 100 Hz EA was more effective than 2 Hz EA. If it is verified that 2 Hz EA is more effective in body weight loss and 100 Hz EA more effective in decreasing plasma lipid content, it may be worthwhile to try the 2/100 Hz alternative mode of stimulation to cover both sides of the disorder.

Effect of EA on Appetite Regulatory Hormones Ghrelin and Leptin

Ghrelin, an endogenous ligand for growth hormone secretagogue receptor, mainly produced by the stomach, is known to increase food intake and body weight [36]. However, in obese human, circulating ghrelin levels were found to be reduced as compared to lean individuals [37]. It was also reported that in obese rodents, ghrelin lost its diurnal fluctuations [38]. All these findings seem to suggest that in obese status, normal function of ghrelin is impaired. In a recent study we found that 2 Hz EA can partly restore the diurnal rhythm of ghrelin in obese rats, accompanied by an effective weight reduction (unpublished data).

Leptin is a peptide known to decrease the body weight and appetite. Kim et al. [39] applied 100 Hz EA to ad libitum fed normal rats and revealed a significant increase of plasma leptin level. You et al. found that 100 Hz EA produced a significant decrease of plasma leptin in obese rats [40]. These results suggest that the effect of EA in modulating plasma level of leptin depends on the energy balance state of the animal. On the other hand, the subject's sensitivity to leptin should be regarded as a more important factor in determining the occurrence of obesity than the plasma level of leptin [39, 40]. In other words, resistance to leptin is more important for the induction of obesity than the insufficient supply of leptin. Therefore, study should be proceeded to characterize whether the sensitivity of leptin can be improved by EA treatment.

Clinical Verification of Laboratory Findings

The literature on acupuncture treatment of obesity use both auricular and somatic acupoints. The mode of stimulation included manual needling, mechanical pressure (acupressure), heating (moxibustion) and transcutaneous electrical nerve stimulation (TENS). We chose to use body acupoints (ST21, ST25, ST28, ST34, SP4) and transcutaneous mode of electrical stimulation with a device entitled "Han's Acupoint Nerve Stimulator (HANS)" which can produce constant current pulses (intensity range 0–50 mA) at frequency range of 2–100 Hz. In an open trial study conducted in the Peking University Health Science Center in Beijing [41], 16 volunteers of the age 20–60, with primary obesity (BMI $\geq$ 25) were recruited, without any instructions or attempts to control their dietary. Each subject received 2 Hz HANS stimulation at eight somatic acupoints distributed mainly in the abdominal area, 3 times per week for 12 weeks. The body weight decreased steadily during the observation period, with a net decrease of 2.06 ± 0.31 kg at the end of 12 weeks treatment, corresponding to a decrease of $2.78 \pm 0.4\%$ of the original body weight ($P < 0.01$). The treatment program was temporarily stopped for 4 weeks (winter vacation for the Chinese New Year), during which a partial (37%) recurrence of the decrement of body weight occurred. In the next 15 weeks the second phase of treatment was implemented. There was again a reduction of body weight up to 2.81 ± 0.68 kg, corresponding to a decrease of $3.90 \pm 0.40\%$ of body weight as compared to the pretreatment level ($P < 0.001$). No significant difference was found in plasma level of cholesterol, triglyceride and glucose before and after the EA treatment. The results suggest that; (1) HANS treatment 3 times a week for 12 weeks produced a moderate but significant decrease in body weight, without any instruction of food restriction or exercise promotion. (2) Termination of treatment for 4 weeks with services of rich food in Chinese New Year produced only a partial (37%) reversal of the body weight. (3) Resumption of treatment remained effective at a similar efficacy. These results imply that a large scale controlled clinical trial is warranted. It is anticipated that a better result may be achieved if (1) 2/100 Hz schedule is used so that not only the appetite but also the fat metabolism may be taken care of, (2) a portable HANS device can be used at home so that the treatment can be continued for longer period of time, and (3) HANS treatment is accompanied with diet control and appropriate exercise.

Conclusions

Evidence obtained from the rat experiment indicated that EA at body points for 30 min produced a significant

reduction of both food intake and the body weigh, with 2 Hz more effective than 100 Hz. EA could also produce a reduction of plasma level of total cholesterol and triglyceride, with 100 Hz more effective than 2 Hz. The appetite suppressive effect of 2 Hz EA is an immediate response, lasting no more than 24 h in the rat. 2 Hz EA stimulation produced an increased expression of the anorxigenic peptides αMSH and CART, and a decreased expression of the orexigenic peptide NPY in the arcuate nucleus of the hypothalamus (ARH) of the rat, which may account, at least in part, the decrease in appetite. EA seems not affecting the energy expenditure by AMPK–UCP3 pathway. An open trial in 16 over-weighted persons showed that 2 Hz transcutaneous electrical acupoint stimulation 3 times a week for 4 weeks produced a steady and significant decrease of body weight. EA resumed after a 4 week break remains effective.

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