

Research Progress of Vestibular Stimulation Regulating Hypothalamus on Obesity

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Abstract. In recent years, the number of obese people in China has increased rapidly, which seriously affects the quality of civil health. In addition to the improvement of living habits, effective intervention measures are urgently needed to prevent and reduce obesity. Vestibular stimulation, as a non-invasive therapy, may improve the conditions of obesity by affecting the hypothalamus. This paper focuses on the causes of obesity and the possible mechanism of vestibular stimulation affecting obesity, aiming to provide new insights into the treatment of obesity.

Keywords: Vestibular stimulation, Obesity, Hypothalamus.

1. Introduction

Obesity is not only a clinical symptom but also a chronic disease. It is characterized by excessive subcutaneous and or visceral fat. It is a high-risk factor for diseases in the metabolic system and cardiovascular system [1], and a variable risk factor for non-communicable diseases [2]. The beneficial effects of reducing obesity include health benefits, improved quality of life, social participation, and economic development [3]. At present, the management strategies for obesity mainly include lifestyle, drugs, and surgery. However, they also bring some problems while improving obesity, such as the short and high probability of weight rebound, although moderate weight loss can be achieved through diet and exercise [4]. Although the U.S. Food and Drug Administration has approved several drugs, due to the lack of data on the long-term cardiovascular effects of these drugs, safety cannot be guaranteed. There are certain risks in surgery, and the acceptability in China is low due to high costs [2]. At present, it is urgent to explore new intervention methods. As a feasible intervention measure, vestibular stimulation seems to avoid these deficiencies, thereby improving the quality of life of service objects.

Vestibular stimulation is mainly divided into natural vestibular stimulation and artificial vestibular stimulation [5]. Natural vestibular stimulation mainly refers to the stimulation generated by the change of posture and posture, such as rotating chairs and sports platforms, while artificial vestibular stimulation mostly stimulates the vestibular system through physical factors such as heat and current. Vestibular stimulation transmits nerve impulses by stimulating vestibular organs such as otoliths and acts on a wide range of nerve structures to regulate related functions. At present, many studies have proved the pathway between vestibular system and hypothalamus. Hypothalamus and other centers can coordinate and control energy balance and glucose homeostasis after integrating a variety of nutrients, hormones, and nerve signals through specific neural pathways. In addition, the hypothalamus can also regulate the response of the gastrointestinal tract through the pathway with the autonomic nervous system. Thus, the vestibular system may affect obesity through hypothalamus. Vestibular stimulation affects the related extensive neural pathways by directly acting on vestibular organs. New studies have found that it may affect obesity by regulating metabolism and energy balance. This article will mainly elaborate on the relationship between the vestibular system and

obesity from three aspects: vestibular stimulation and adipose tissue, vestibular stimulation and diet intake, vestibular stimulation, and energy balance, in order to provide a new clinical idea for the improvement of obese conditions.

2. Formation and regulation of obesity

An objective cause of obesity is the generation of positive energy balance, that is, the intake of energy exceeding the energy consumed by maintaining life and physical labor [6]. Energy balance is a dynamic model [7], which can be realized not only at different levels of body weight and body composition but also at different levels of energy intake and energy consumption. Taking adipose tissue as an example, the adipose tissue in mammals mainly includes white adipose tissue (WAT) and brown adipose tissue (BAT). The main function of white adipose tissue is to store excess energy and secrete various hormones and metabolites to regulate the energy balance of the body [8]; The main function of brown adipose tissue is to participate in most non-shivering thermogenesis heat production and consume energy in the form of heat energy [9]. WAT mainly used to store energy can turn into beige adipose tissue, which has a certain effect on energy consumption similar to BAT. When excessive dietary intake leads to chronic excess calories, adipose tissue will proliferate and hypertrophy, leading to inflammation of white adipose tissue, resulting in weight gain and obesity [10]. James [11] et al. summarized the energy intake and consumption in the research data in recent decades and roughly estimated that the weight gain calculated according to the research is much more than the actual situation, which shows that weight or obesity cannot be understood merely as the result of the process of energy intake and consumption offsetting. To a certain extent, it shows that the establishment of human energy balance is regulated by the body.

2.1. Response and regulation of gastrointestinal tract

In addition to the most basic role of a digestive diet, the gastrointestinal tract also plays a key role in the regulation of energy balance. Gastrointestinal-derived signals, including various peptide hormones, bile acids, and intestinal microbiota molecules derived from intestinal epithelial cells, can convey information about nutrients introduced [12] and mechanical stimulation of intestinal receptors by food intake [13]. These signals from the intestine can coordinate various organs involved in digestion and provide the brain with key information about the energy content of nutrient intake.

Intestinal endocrine cells are the main sensors for nutrient intake. They synthesize and release a series of peptides and hormones as autocrine, paracrine, or endocrine regulators of digestive function, glucose homeostasis, and energy balance. Cholecystokinin (CCK), a typical gastrointestinal satiety peptide, can acutely inhibit food intake. CCK exerts anorexia through a paracrine mechanism, involving the effect of CCK1 receptor (CCK1R) on vagal afferent, which projects to the relay station solitary nucleus and then to the paraventricular nucleus of the hypothalamus [14]. Rats lacking CCK1R will consume too much food and produce obesity [15]. The mechanism may be that CCK cannot affect the vagus nerve to complete the projection to the paraventricular nucleus of the hypothalamus through *cck1r*, so it cannot normally play the role of anorexia, leading to obesity.

Besides CCK, leptin also plays an important role in food intake. Leptin is expressed and secreted into the gastric cavity in gastric master cells and gastric endocrine cells [16]. Gastric leptin is involved in the short-term regulation of food intake, which is rapidly secreted by the vagal nerve in response to food intake and peptide hormones, such as CCK and insulin. Leptin receptor exists in gastric vagus nerve afferent, and the response of gastric vagus nerve afferent to leptin depends on the dynamic response of nutritional status. Leptin receptor exists in gastric vagus nerve afferent, and the response of gastric vagus nerve afferent to leptin depends on the dynamic response of nutritional status. Under fasting conditions, leptin inhibits gastric tension-sensitive vagus nerve afferents and promotes food intake. On the contrary, in the dietary state, leptin has an exciting effect on gastric vagus nerve afferents [17]. Lartigue [18] et al. fed rats with the same initial weight with conventional feeding and a high-fat diet, respectively. The results showed that the fasting plasma leptin level of diet-induced

obese rats was significantly higher than that of other groups, and Vagal afferent neurons (VAN) increased the expression of cytokine signal transduction inhibitory factor 3 (SOCS-3), which may be the reason for leptin resistance in these rats. In addition, the levels of leptin and lipopolysaccharide increased in the circulation, which may be the mechanism of leptin resistance in vagus nerve afferent neurons.

The gastrointestinal tract will respond directly to diet, mainly through enteral nutrients and gastric tension signals, and then through the vagus nerve to neurons, which are first uploaded to the brain stem, and then further transmitted to the central nervous system, especially the relevant nuclei of the hypothalamus, to make corresponding adjustments to satiety and dietary intake. When there is a problem in the secretion and or transmission pathway of these hormones, so that the dietary signal cannot be transmitted correctly, it may lead to obesity.

2.2. Regulation of central nervous system

The structure of the central nervous system, especially the neural pathways in the hypothalamus, integrates a variety of nutrients, hormones, and neural signals to coordinate and control energy balance and glucose homeostasis [19]. Both energy balance and glucose homeostasis affect obesity. Carlos [20] et al. showed that glucose tolerance was related to central obesity. The central nervous system can regulate appetite, satiety, food intake, and metabolism by regulating the neuroendocrine system, and ultimately achieve the regulation of energy balance. The neuroendocrine system consists of numerous brains, intestinal, pancreatic, and adipose tissue hormones that bind to receptors in the peripheral and central nervous systems, especially in the hypothalamus and thalamus [21].

Leptin is the hormone most related to energy balance regulation [22]. Leptin is uploaded to the central nervous system through the vagus nerve. It provides the brain with a signal of fat storage and energy balance and mediates a complex neural signal regulation system. This system regulates the signal related to energy homeostasis by integrating intestinal derived hormones, glucose, insulin, and free fat, thereby affecting the development of brain regions related to neuroendocrine function, autonomic nerve, and eating behavior. Moreover, leptin receptors are highly expressed in hypothalamic nuclear cells, which play an important role in weight regulation. In the hypothalamus, multiple nuclei are associated with other areas of the brain associated with reward and satiety. Leptin can regulate the activities of the reward pathway and reduce food intake by reducing the hedonic value of food. Therefore, insufficient leptin secretion or leptin resistance will cause obesity; Leptin can also regulate dietary intake and body composition through its effect on satiety-related centers, so as to regulate energy balance.

Energy intake and consumption are also controlled by neuropeptide hormones produced by the central nervous system. The arcuate nucleus (ARC) of the hypothalamus can express proopiomelanocortin (POMC) and simultaneously release the agouti-related protein (AgRP/neuropeptide Y, NPY neurons), which has long been considered the main central regulator for maintaining energy balance. POMC neurons synthesize and secrete an anorexia peptide, namely α -melanocyte-stimulating hormone (α -MSH). α -MSH can activate the melanocortin-4 receptor, reduce appetite and increase energy consumption to prevent overeating and weight gain [23]. On the contrary, AgRP / NPY neurons inhibit the melanocortin-4 receptor, which can increase appetite and reduce energy consumption [24]. AgRP neurons seem to exert a unidirectional and forced inhibitory effect on POMC neurons, which means the neuroanatomical tendency of positive energy balance, leading to the development of metabolic syndrome such as obesity. Inhibitory AgRP neurons locally project to POMC neurons, and their targets involve many brain regions, including the hypothalamic paraventricular nucleus, thalamic paraventricular nucleus, parabrachial nucleus, bed nucleus of stria terminalis, lateral hypothalamic area, and medial amygdala. Studies have shown that the hypothalamic paraventricular nucleus, bed nucleus of stria terminalis and lateral hypothalamus can trigger eating behavior when projected by AgRP axons [25] [26]. Generally speaking, some specific nuclei of hypothalamus regulate human feeding behavior and energy balance under the action of specific hormone signals such as leptin and neuropeptide hormone.

3. The possible mechanism of vestibular stimulation affecting obesity

3.1. Vestibular system and adipose tissue

Adipose tissue is an important part of body composition, and it also plays a certain role in energy regulation. In addition to energy consumption in the form of heat, BAT has great potential in the absorption and treatment of glucose, which can be involved in regulating glucose homeostasis [27]. There is such a model for the regulation of glucose homeostasis: glucose supplements the intracellular triglyceride pool, which provides fatty acids required for heat production [28], that is, the regulation of glucose homeostasis also involves the regulation of energy. BAT's role in energy consumption and regulation of glucose homeostasis and the browning of WAT provide a new idea for the treatment of obesity. The activation of the sympathetic nerve promotes the decomposition of lipids in white adipose tissue and the production of heat in BAT [29]. Therefore, the vestibular system may regulate adipose tissue through the sympathetic nervous system, directly act on BAT, and or promote wat browning, so as to increase energy consumption and regulate glucose homeostasis, thereby improving obesity.

The regulation of vestibular system on the autonomic nervous system has been confirmed. Although most of them are focused on cardiovascular and respiratory responses [30] [31], experimental studies have emphasized the interaction between the vestibular system and the hypothalamus. Azzena [32] et al. Found that the electrode probe placed in the hypothalamus of guinea pigs could detect the activation of neurons after electrical stimulation of the vestibular nerve about 30 years ago, and then proved that vestibular nerve stimulation could induce the effective activation of lateral hypothalamic nucleus and nucleus solitarius in mammals such as rabbits [33].

Patrick [34] et al. conducted 8 - week vestibular stimulation on mice by centrifugation, and found that the initial food intake and long-term body fat of mice were reduced, but these characteristics were not obvious in mice lacking macular otolith. This animal experiment demonstrates the effect of vestibular stimulation on body composition, especially adipose tissue. The mechanism is the connection between the vestibular system and the hypothalamus, because there are neuronal circuits responsible for feeding and autonomic nervous system functions in the hypothalamus. The autonomic nervous system (ANS) plays a direct control role at the cellular and molecular levels of obesity. The sympathetic nervous system can increase or reduce the sympathetic outflow to the fat bank according to the body condition. The parasympathetic nervous system regulates insulin-mediated glucose uptake and fatty acid metabolism in adipose tissue in the way of anabolism [35]. The hypothalamus ensures adaptive changes in normal eating and movement by mechanisms of changing various neural and endocrine effectors, including the balance between sympathetic and parasympathetic outflow [32].

Studies have shown that the ventromedial hypothalamic nucleus and lateral hypothalamic nucleus are involved in BAT regulation. Repeated drug stimulation of the hypothalamic arcuate nucleus can lead to subcutaneous WAT browning, thereby improving glucose treatment [36]. Similarly, reducing the appetite-promoting AgRP neurons in the arcuate nucleus increases the visceral norepinephrine concentration by reducing its inhibitory effect on POMC neurons, thus promoting WAT browning and improving glucose tolerance.

Therefore, from the current relevant research, the most possible way for vestibular stimulation to regulate body composition is through the hypothalamus. The hypothalamus realizes the metabolic regulation of adipose tissue through the autonomic nervous system and promotes heat production and energy consumption by acting on bat or promoting wat browning, so as to improve obesity. In addition, the hypothalamus can also affect the intake of nutrients by regulating eating behavior, to realize the regulation of body components.

3.2. Vestibular system and dietary intake

In addition to regulating adipose tissue through the autonomic nerve pathway, the hypothalamus can also regulate body composition and body weight through the central regulation of feeding. It is

generally believed that the lateral hypothalamic area (LHA) is the main neural structure that initiates feeding, that is, the hunger center, while the ventromedial hypothalamic nucleus (VMH) of the hypothalamus is the satiety center. Their functions restrict each other, and their dysfunction leads to abnormal feeding behavior. The normal realization of hypothalamic regulation of diet will be affected by leptin and the thyroid system.

3.2.1 Leptin

Leptin is secreted by adipose tissue and acts as an afferent signal in the negative feedback loop, mainly by acting on hypothalamic neurons and regulating eating behavior and other functions. The effects of leptin on dietary intake are mainly achieved through the following ways. One is that leptin regulates food intake and weight by stimulating POMC neurons and inhibiting NPY / AgRP neurons in hypothalamic arcuate nucleus. When AgRP neurons are active, they will transmit the unpleasant sensation of hunger and enhance the motivation of eating. Food intake can inhibit the activity of NPY / AgRP neurons and reduce the unpleasant sensation [37]. Leptin can also regulate the activities of reward pathways, in part by reducing food intake by reducing the hedonic value of food. The author Domingos proved by photogenetic analysis that leptin can reduce the activation of dopaminergic neurons by sucrose in the ventral tegmental area of the midbrain, so as to reduce food intake by reducing the desire for food intake [38].

The downstream target of leptin action is neurons expressing the melanocortin-4 receptor (MC4-R). The central melanocortin system has been clearly defined as a key regulator of energy homeostasis, which can regulate the eating behavior and body weight of humans and animals. Wang Yi [39] et al. found that the activation of MC4-R increased the activity of adenylate cyclase, so that the cilia in the paraventricular nucleus of the hypothalamus could normally limit food intake; On the contrary, inhibition of adenylate cyclase activity in cilia or cilia removal can lead to overeating and obesity. What's more, MC4-R neurons in the hypothalamic paraventricular nucleus can also sense the balance of appetite-inducing AgRP and anorexic melanocortin signals [40], and then regulate eating behavior and energy consumption.

Kathleen [41] et al. used the immunohistochemical method to study the expression difference of leptin receptor (OBR) between the estrogen treatment group and the control group under the assumption that leptin may participate in ear labyrinth. The results showed that in the control group, OBR immune markers were not detected in ear capsule bone, but in cochlear vestibular nerve, while in the estrogen treatment group, positive OBR immunolabeling was observed in osteoblasts in the new bone of the ear capsule, and OBR labeling in cochlear vestibular nerve decreased. Also, the weight gain of the control group was significantly higher than that of the treatment group. These results suggest that the vestibular system, especially the vestibular nerve, is closely related to leptin in physiology and anatomy, so vestibular stimulation has an anatomical pathway to affect obesity through leptin.

In a clinical experiment, Sai sailesh [42] et al. randomly divided 30 patients with type 2 diabetes into two groups. The intervention group received electrical vestibular nerve stimulation (VeNS) for 90 days, while the control group received false stimulation for 90 days, which used a false device that emitted beeps and flashes but did not transmit effective stimulation. The results showed that the fasting, postprandial blood glucose, and low-density lipoprotein levels of leptin in the intervention group were significantly decreased after 30-day and 90-day VeNS treatment, and the weight loss in the intervention group was statistically significant compared with the control group. The results showed that the multiple effects of vestibular stimulation could not only regulate glucose metabolism, but also the activities of the autonomic nerve. The weight loss caused by vestibular nerve stimulation may be mediated by the vestibular nerve affecting the normal transmission of leptin signal and further affecting the hypothalamic nucleus controlling appetite, so as to reduce appetite. Therefore, it is possible to improve obesity by mediating leptin and the central pathway through vestibular stimulation.

3.2.2 Thyroid system

Thyroid hormone (TH) plays an important role in eating behavior by directly affecting the central mechanism involved in the regulation of energy metabolism. Luis [43] et al. demonstrated that hyperthyroidism rats showed significant up-regulation of hypothalamic mammalian target of rapamycin (mTOR) signaling pathway, which was related to the increased mRNA level of AgRP / NPY and the decreased mRNA level of POMC. Although it is generally believed that the increase of appetite is to compensate for negative energy balance, the latest evidence shows that the effect of TH on dietary intake is autonomous and independent. One of the main targets of thyroid hormone is the arcuate nucleus of the hypothalamus. They can independently affect eating by targeting ARC of the hypothalamus. Triiodothyronine, one of the main active substances secreted by TH, can induce the increase of anorexic neuropeptide AgRP / NPY neurons and the decrease of POMC leading to anorexia [44], resulting in the overall effect of promoting dietary intake.

Many clinical studies have explored the relationship between thyroid disease and vestibular system function as early as decades ago. Hypothyroidism may affect different parts of the vestibular system. Severe congenital hypothyroidism is associated with central vestibular disorder of the cerebellum, while mild hypothyroidism is associated with peripheral vestibular disease [46]. Recently, So Young Kim [45] and others used an embedded case-control study to find the association between Meniere's disease and thyroid disease. The results showed that there were significant differences in the distribution of obesity, benign paroxysmal vertigo, vestibular neuritis, and other peripheral vertigo between the Meniere's disease group and the control group, and the history of various thyroid diseases was highly correlated with Meniere's disease. With regard to the relevant mechanisms of these connections, the authors speculate that the inflammatory or metabolic changes in patients with thyroid diseases may affect the inner ear inflammation and the homeostasis of endolymphatic flow, and Meniere's disease may affect thyroid diseases through the autoimmune pathway. The oval sac, balloon and semicircular canal are important vestibular organs in the inner ear, so the pathway and relationship between the vestibular system and thyroid system can be roughly determined.

The animal study has shown that cold or heat stimulation of the vestibule of rats in the stress environment induced by cold water swimming can prevent excessive changes in thyroid function, cholesterol, and body weight mediated by stress within 15 days [46]. Although the article does not clarify the mechanism too much, we can roughly infer that this may be mediated by affecting the hypothalamic control of appetite through the thyroid system or other related pathways.

3.3. Vestibular system and energy balance

In fact, the changes in body composition and the regulation of dietary intake mentioned above affect the establishment of energy balance more or less. Leptin endocrine system plays a key role in energy balance by regulating appetite and maintaining the relative constant mass of adipose tissue, so as to reduce the risk of individual obesity. Disorders of the thyroid system will not only significantly regulate body temperature, insulin resistance, and secretion delay, but also significantly regulate energy consumption and appetite, resulting in changes in human metabolic state and body composition [47].

In terms of neural anatomy, melanocortin neurons in the medial vestibular nucleus (MVE) were found [48], and MVE can project to POMC neurons in the nucleus solitarius; At the same time, prolyl carboxypeptidase, which plays an important role in the regulation of melanocortin signal, is expressed in the medial vestibular nucleus and the lateral vestibular nucleus [49]. In short, the vestibular nervous system, especially the vestibular nucleus, has established a close relationship network with the melanocortin system, and the central melanocortin system can regulate the energy balance by regulating the eating behavior and body weight of humans and animals. In addition to the close relationship between MVE and the melanocortin system, animal experiments show that MVE is also one of the areas controlled by the sympathetic nerve center [50]. Thus, the vestibular system can regulate adipose tissue and other body components through the pathway of the sympathetic nervous system, so as to regulate energy balance.

In a clinical study, Marco [51] and other researchers compared the energy consumption and exercise behavior of patients with chronic unilateral vestibular dysfunction (UVH) with healthy participants. The evaluation tool was a wrist physical activity tracker, which was analyzed with bioelectrical impedance. The results showed that the energy consumption of resting and exercise daily life of UVH subjects was significantly lower than that of the control group. This may be because chronic vestibular afferents affect the activity of the melanocortin system along the central vestibular pathway, thereby affecting energy consumption.

In short, the vestibular system can regulate dietary intake, body composition, and energy consumption in a variety of ways, which can further affect the establishment of energy balance, and then affect obesity.

4. Summary and outlook

This paper mainly discusses the formation and regulation of obesity and the possible mechanism of vestibular stimulation affecting obesity. The possible mechanism of vestibular stimulation affecting obesity mainly includes the relationship between vestibular stimulation and adipose tissue, dietary intake, and energy balance. In these mechanisms, hypothalamus plays an important role. The neural pathways between the vestibular system and the hypothalamus have been confirmed, while human appetite, satiety, food intake and metabolism are regulated by the central system, especially the hypothalamus, thereby affecting the establishment of energy balance. Studies on the vestibular system and autonomic nervous system in cardiovascular and respiratory fields show that there is a close relationship between the vestibular system and autonomic nervous system, but there is a lack of relevant research on the impact of the vestibular system on the gastrointestinal tract. Therefore, the most likely mechanism of vestibular stimulation on obesity is based on the connection between the vestibular system and hypothalamus, and then through the further regulation of the hypothalamus.

At present, the most common way to lose weight is to control diet and exercise, but their continuity is poor, and patients often cannot adhere to them constantly. Under the theoretical guidance of the mechanism of vestibular stimulation, several drugs are also approved for the treatment of obesity for the regulation of brain centers involved in energy homeostasis [52]. However, their use is also limited due to the fear of side effects. At present, two neuromodulatory devices can be used to treat obesity, Maestro targeting the vagus nerve and abiliti system targeting the gastric parietal nerve [53]. However, both devices need surgical implantation, and due to the risks, they are limited to the most obese patients according to relevant laws and regulations. Based on the limitations of these therapies, there is an urgent need for more practical and better methods.

Through the description of this paper, the possibility of vestibular stimulation affecting and even improving obesity can be seen. If this idea is further verified and confirmed, it will constitute a new, nonpharmacological and non-invasive treatment of metabolic syndromes.

However, some studies on vestibular stimulation are mainly based on animal experiments, and there are few relevant clinical studies. The neural pathway and hormone regulation of vestibular stimulation through the hypothalamus in obesity are complex and extensive, and a perfect and definite mechanism theory has not been formed at present. Therefore, the author expects more basic or clinical researches on the relationship between vestibular stimulation and obesity in the future, so as to add new insights to the treatment of obesity.

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