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Stimulation of sympathetic innervation in the upper gastrointestinal tract as a treatment for obesity

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SUMMARY

Sympathetic activity and obesity have a reciprocal relationship. Firstly, hypothalamic obesity is associated with decreased sympathetic activity. Caffeine and ephedrine increase sympathetic activity and induce weight loss, of which 25% is due to increased metabolic rate and 75% is due to a reciprocally decreased food intake. Secondly, hormones and drugs that affect body weight have an inverse relationship between food intake and metabolic rate. Neuropeptide Y decreases sympathetic activity and increases food intake and body weight. Thirdly, a gastric pacemaker Transcend® and vagotomy increase the ratio of sympathetic to parasympathetic activation, decrease food intake, and block gut satiety hormones. Weight loss with the pacemaker or vagotomy is variable. Significant weight reduction is seen only in a small group of those treated. This suggests that activation of the sympathetic arm of the autonomic nervous system may be most important for weight loss. Systemic sympathetic activation causes weight loss in obese patients, but side effects limited its use. We hypothesize that selective local electrical sympathetic stimulation of the upper gastrointestinal tract may induce weight loss and offer a safer, yet effective, obesity treatment. Celiac ganglia delivers sympathetic innervation to the upper gastrointestinal tract. Voltage regulated electrical simulation of the rat celiac ganglia increased metabolic rate in a dose-dependent manner. Stimulation of 6, 3, or 1.5 V increased metabolic rate 15.6%, 6.2%, and 5%, respectively in a single rat. These responses support our hypothesis that selective sympathetic stimulation of the upper GI tract may treat obesity while avoiding side effects of systemic sympathetic activation.

Introduction

Support for our hypothesis that sympathetic stimulation of the upper gastrointestinal tract may offer a safe and effective treatment for obesity comes from four general lines of evidence.

Hypothalamic obesity

Vagotomy can prevent hyperinsulinemia and obesity from hypothalamic damage in humans [38]. Rodents and humans with hypothalamic obesity show increased parasympathetic tone with augmented vagal activity, impaired responses of the sympathetic nervous system, decreased energy expenditure, and endocrine changes [9,25,31,38,41]. Human hypothalamic obesity was first reported by Frohlich [19], Bruch [11], and Babinski [4] at the beginning of the 20th century. Erdheim published one of the first collections of cases in 1904. The pathology showed damage to the medial hypothalamus, excluding the pituitary [17]. A collection of 134 patients, including eight original cases, were reported in l975 [9]. An autopsy report by Reeves and Plum [33] showed that this syndrome was associated with bilateral injury to the ventromedial (or paraventricular) nuclei of the hypothalamus. Ventromedial nuclei control body weight. Destruction of these areas removes tonic inhibitory influences on traffic through the vagus nerve. The increased parasympathetic (vagal) tone elevates insulin release, increases food intake, and facilitates energy storage in adipose tissue [7]. Placing the islets under the kidney capsule removes them from vagal control, reverses the hyperinsulinemia resulting from hypothalamic damage, and prevents the development of obesity [24].

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Leptin receptors are expressed in the hypothalamus. As in all obesities, leptin levels are high in hypothalamic obesity. The leptin responses, however, are reduced in hypothalamic injury due to damage to the leptin receptors. Hypothalamic obesity in humans, however, is uncommon.

In experimental animals, injury to the arcuate nucleus complex, ventromedial hypothalamic area, paraventricular nucleus or central nucleus of the amygdala increase food intake and obesity. The obesity occurs to some degree even when hyperphagia is prevented [26] in these animals with nervous system damage. Likewise, the injury is associated with an acute increase of vagal activity [5,23,27,39] accompanied by a decreased sympathetic activity [29,34,40,42].

Sympathetic activity in obesity

Low sympathetic activity is common in obesity of various etiologies including hypothalamic obesity [6]. An inverse relationship between sympathetic activity and food intake, and a direct relationship between sympathetic activity and metabolic rate are present [8]. Recently, an 18-year follow-up study demonstrated that lower sympathetic activity increased body fat over time [18].

Sympathetic activity is decreased in leptin deficiency and in other genetic mutant obesity. In leptin deficient mice, stimulation of the sympathetic innervation to brown adipose tissue results in less heat production than in lean littermates suggesting a reduced sympathetic activity [36]. The sympathetic activation seems to be mediated by cortocotrophin releasing factor (CRF) produced in the central nervous system (CNS) acting on the adrenal–pituitary circuit. Adrenalectomy reduces glucocorticoid feedback to the hypothalamus and increases the CRF that, in turn, stimulates the sympathetic nervous system. Thus, adrenalectomy stops the progression of obesity in *ob*/*ob* mice [10]. Diminished sympathetic activity is also seen in the yellow mouse that is obese as a consequence of overexpression of agouti-related protein. These data support that sympathetic activity is decreased as consequences of abnormalities in the CRF-pituitary–adrenal system that are present in the yellow mouse, *ob*/*ob* mouse, *db*/*db* mouse and the *fa*/*fa* rat, all of which have genetic defects in the leptin system or in agouti-related peptide [10,37]. Similarly, the reciprocal relationship of sympathetic activity to food intake takes place in normal humans as well. In an 18-year follow-up study, arterial plasma epinephrine and norepinephrine concentrations were measured in 99 healthy men during mental stress and baseline at rest. The data demonstrated that an increase in BMI and waist circumference are inversely related to the epinephrine and norepinephrine responses in the mental stress group compared to baseline ($P < 0.05$) [18]. The inverse relationship has also been shown when various drugs and hormones that affect body weight are administrated. Neuropeptide Y, β-endorphin, norepinephrine, and 2-deoxyglucose stimulate food intake and reduce sympathetic activity while enterostatin, glucagon, sibutramine, and amphetamine decrease food intake and increase sympathetic activity [8].

Sympatomimetic agents have shown some efficacy in the treatment of obesity. Clinical observations demonstrated that ephedrine stimulates β-adrenergic receptors to increase energy expenditure and decrease food intake [2]. Caffeine inhibits phosphodiesterase and adenosine receptors which otherwise blunt the effect of ephedrine [16]. Thus, a combination of ephedrine 20 mg and caffeine 200 mg three times a day was developed to treat obesity. Three hypothalamic obese patients lost an average of 10% of their body weight over 6 months when treated with the combination [21]. In a registration trial in Denmark to approve this combination for the treatment of obesity, the ephedrine and caffeine treated subjects lost 17.5% of initial body weight which was significantly greater than the placebo treated patients. A 13.6% of weight lost was seen in the placebo group, which is believed to be due to diet and nutritional consultation during the trial resulting in such a large loss in the placebo group [1]. In the case series of three hypothalamic obesity patients, without a stringent diet and nutritional counseling, all of the subjects with hypothalamic obesity lost less than 15% of their body weight with the combination. Unfortunately, acute side effects of nervousness, insomnia, rapid heartbeat, blood pressure elevation, and nausea were disadvantages of medication causing systemic sympathetic activation with ephedira, and these side effects resulted in the withdrawal of herbal caffeine from the unregulated dietary herbal supplement market by the US Food and Drug Administration [15,20].

Gastric pacemaker

Selective, rather than systemic, autonomic activation by electrical pacing for the treatment of obesity began in 1996 [14]. The Transcend® gastric pacemaker which stimulates the vagal innervation of the stomach is placed laparoscopically on the lesser curature of the stomach for the treatment of obesity [22]. The average weight loss in an unselected cohort of morbidly obese subjects was 10 kg [13]. Interestingly, a small group of subjects showed 30% weight loss, which is equivalent to the gastric bypass, an operation that gives durable weight loss over years of follow-up [13,22,32]. Increased vagal efferent activity elevates GI satiety hormones cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and somatostatin, which is blocked by vagotomy [13]. All three of these hormones are associated with a decrease in food intake and they are paradoxically decreased by gastric stimulation [13]. The effect of the Transcend® pacemaker is believed to act through the vagal afferent signals to the brain and block the GI satiety hormones secretion mediated by efferent vagal activity. These and other stimulation data suggest that the local stimulation suppressed efferent and stimulated afferent vagal traffic to induce weight loss [12]. A similar variability of weight loss is seen with vagotomy as with the Transcend® gastric pacemaker [28]. This suggests to us that the ratio of sympathetic to parasympathetic activation is directly related to weight loss. One can consider that a predominance of vagal efferent overactivity causes obesity in the population that display 30% weight loss. By the same token, interruption of the efferent vagal pathway either by vagotomy or by vagal afferent stimulation causes significant weight loss in a small group of those treated. Taken together, both the sympathetic underactivity and the vagal overactivity may play an important role in perpetuating obesity. Thus, the ratio of sympathetic to parasympathetic activity would actually correlate better with obesity than either arm of the autonomic nervous system alone.

The hypothesis

We hypothesized that selectively stimulating the sympathetic nervous system that innervates the GI tract will have the potential to elevate metabolic rate while avoiding the systemic side effects.

Evaluation of the hypothesis

It is known that caffeine and ephedrine increase sympathetic tone and metabolic rate 19% over 3 h [2] and ephedrine increases metabolic rate 2% on an energy restricted diet measured in a metabolic chamber over 24 h [30]. Of the weight loss seen with caffeine and ephedrine, 25% is attributable to an increase in metabolic rate while 75% is due to a decrease in caloric intake [3]. However, the systemic stimulation of the cardiovascular and central nervous systems seen with caffeine and ephedrine resulted in their withdrawal from the non-prescription market [15].