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IS THE VAGUS NERVE STIMULATION A WAY TO DECREASE BODY WEIGHT IN HUMANS?

Abstract: *Is the vagus nerve stimulation a way to decrease body weight in humans?*
Obesity and its complications constitute an important health problem in growing number of people. Behavioral and pharmacological treatment is not much effective and surgical treatment carries too many threats. Promising method to be used is pharmacological or electric manipulation of vagus nerves.

Regulation of food intake and energy utilization is a complex process regulated by centers in hypothalamus and brainstem which are receiving information from the peripheral via afferent neural pathways and sending peripherally adequate instructions by efferent neural pathways. In these signals conduction an important role plays vagus nerve. Additionally central nervous system stays under influence of endocrine, paracrine and neuroendocrine signals taking part in these regulations, functioning directly onto the centre or on the afferent neural endings. 80–90% fibers of vagus nerve are afferent fibers, so their action is mainly afferent, but possible contribution of the efferent fibers cannot be excluded. Efferent stimulation induces motility and secretion in the intestinal tract. Afferent unmyelinated C-type fibres of the vagus nerve are more sensitive and easily electrically stimulated. Information from vagus nerve is transmitted to nucleus tractus solitarius, which has projections to nucleus arcuate of the medio-basal hypothalamus, involved in the control of feeding behavior.

It is suggested, that interaction onto the vagus nerve (stimulation or blocking) can be an alternative for other ways of obesity treatment. Through the manipulation of the vagus nerve activity the goal is achieved by influence on central nervous system regulating the energy homeostasis

Keywords: vagal afferent nerves, vagal modulation, vagus nerve stimulation, vagotomy, appetite, obesity, body weight

ROLE OF VAGUS NERVE IN WEIGHT CONTROL

Vagus nerve (VN), i.e. cranial nerve X, constitute a very important input to central nervous system (CNS) entering the peripheral information particularly from digestive tract. In 80–90% it is a sensory nerve [1, 2]. Vagus nerve is responsible for the transmission of the majority of the afferent signals responsible for satiety [3, 4]. Afferent pathway of gut-brain axis has a direction via afferent fibers of vagus nerves and spinal nerves (sympathetic) and is transducing information into the brain from stimulated receptors sensitive to various types/kinds of

stimulation: 1. mechanical — sensitive to changes in tension of gastrointestinal tract walls; 2. chemical — reacting to nutrients (food ingredients) in the gut lumen, and 3. neurohormonal stimuli such as gut hormones, neurotransmitters, neurostimulators, inflammatory mediators [5].

It has been demonstrated in rats that gastric distension increases vagus nerve activity [6]. Distension of either the stomach or the duodenum is one of the factors stimulating satiety [6].

Vagus nerve transmits centrally signals from mucosa stimulated by jejunal fatty acid infusions, what have been described in cats [7] and then in other animals [8, 9]. Vagotomy or capsaicin, component of chili peppers that selectively destroys vagal afferent fibers, eliminates decreasing appetite effect of fatty acids given into duodenum, while the effect of glucose given into duodenum is weaker, indicating that the control of glucose blood level remains under brain control.

Schwartz et al. demonstrated that combinations of gastric load and exogenous peptides excited gastric vagal mechanoreceptors to a greater degree than either stimulus alone [10]. These data indicate that individual gut vagal afferents possess distinct transduction mechanisms for the different classes of meal-related negative feedback signals, and can simultaneously integrate these signals to send a coherent message regarding meal size to the intake-regulation centre in the brain. Vagal afferent neurons, that synapse in the nucleus tractus solitarius (NTS) in the hindbrain, can integrate different information such as gastric distension, the luminal chemical environment, microbiota, and tissue health. That is why vagal afferent stimulation is involved in the control of food intake, gastric emptying, secretion from the stomach and pancreas [5].

VN also transmits different signals than these mentioned above. A variety of receptors for ligands with orexigenic (hunger, i.e. those stimulating appetite) and anorexigenic (satiety, i.e. those inhibiting appetite) properties have been identified on the vagal afferents.

Stimulation of serotonin receptor ($5\text{-}HT_3$), cholecystokinin receptor (CCK_1), vanilloid (capsaicin) receptor (VR_1), tachykinin receptor (NK_1) increases, but stimulation by ghrelin, leptin, kappa-opioid and receptors for gamma-aminobutyric acid ($GABA_B$) receptors decreases vagal activity [11].

Vagal afferent neurons are a primary target of CCK. Part of secreted CCK diffuses locally paracrinally and stimulates receptors CCK-A on vagal afferent neurons, ending in NTS [12–14]. Resistance to CCK occurs in obesity and is one of mechanism of food intake regulation changes in obesity. Vagotomy attenuates the response of the CCK on reduction of food intake. Ghrelin receptors are found on sensory fibers of the vagus nerve and can thus relay a signal to eat more to the CNS via peripheral nerves [15]. Vagus nerve circuits play a role in leptin secretion. Cigaina and Hirschberg reported decrease in leptin level significantly correlated with weight loss in patients with gastric pacing [16]. Wang and Liu did not find any changes in leptin level neither after vagus nerve dissection nor

after gastric bypass in rats [17]. However, leptin concentration was significantly diminished and correlated with weight loss in both studies. De Lartigue et al. demonstrated that diet-induced obesity leads to the development of leptin resistance in vagal afferent neurons and leptin signaling in vagal afferent neurons is required for appropriate cholecystokinin signaling and satiation, limiting meal size and duration [18, 19].

Y_2R receptors for Peptide YY (PYY), an appetite suppressing hormone [20], are expressed on the VN [21]. Anorectic effect of PYY_{3-36} on food intake is abolished following subdiaphragmatic truncal vagotomy. PYY acts centrally inhibits gastric emptying and motility [22]. Pancreatic polypeptide (PP), another polypeptide from the "PP-fold" family of proteins, may act via vagus nerve, and the anorectic effect of it is abolished by vagotomy in rodents [23].

VN takes part in mediating signal via Glucagon-Like Peptide-1 (GLP-1) for food intake [20].

It has been reported that expression of receptors on vagal afferent neurons is modulated by diet, for example in nodose ganglia of mice fed a high fat diets decreased expression of CCK_1 receptors has been reported [24]. It was also shown that both caloric restriction and high fat diet decrease mechanosensory vagal afferent signals in mice, and augment the inhibitory effect of ghrelin on vagal afferents, but different mechanisms mediate the short- and longer-term changes [25].

Vagus nerve also regulates guts' absorption, its motility and energy utilization (feed efficiency) on the central level. Rats with electrical vagus nerve stimulation (VNS), on the cervical level, to gain their weight of 1 gram needed more kcal than control rats [26]. Mobilization of free fatty acids (FFA) from fat during VNS have been shown [26].

Left and right trunks of the VN have different distributions. Left (frontal) one has a hepatic branch of the vagus nerve, which is an important source of afferent input controlling both physiological and behavioral homeostasis. Liver detects changes in its energy and can transmit information regarding these changes into brain via VN. Evidences also exist, that liver is responsible for fatty acids and their metabolism fluctuations by sending signals to the brain with the help of VN [27]. Electrophysiological experiments showed most direct stimulation of the vagal sensory neurons. Niijima by extracellular recording showed that infusion of glucose and other nutrients, hormones and other factors stimulated VN [28, 29].

General concept, that VN plays an important integrative role in short-term regulation of food intake is still valid [30].

Electrical stimulation of the vagus nerve engages vagal afferents which mediate satiety signals from the gastrointestinal tracts. Experiments on animals have been started with the aim to explain whether VNS on the thoracic and abdominal level changes gut motility and absorption.

Vagus nerve stimulation (VNS) increases, in different brain regions, secretion of brain-derived neurotrophic factor (BDNF), which has been identified as a key component of pathways that controls body weight and energy homeostasis [26].

Das proposed that VNS could be of significant benefit in metabolic syndrome, because VNS has been shown to suppress inflammation and reduces insulin resistance [31]. Efferent stimulation of vagus nerve inhibits inflammation and enhances cholinergic signaling within the inflammatory reflex, can suppress obesity-associated inflammation and its adverse implications [32].

Vagus nerve takes part in maintaining glucose homeostasis via its fibres components in liver, pancreatic β cells and hypothalamus. Species with resistance to insulin and metabolic syndrome developed subnormal vagal tone with high sympathetic one, which effect in low-grade systemic inflammation. The main vagal neurotransmitter, acetylcholine, inhibits proinflammatory cytokine release and thus suppresses inflammation.

We previously showed that electrical vagus nerve stimulation decreases food intake and body weight in rats with short-term [33] and chronic vagal stimulation [34–36].

ROLE OF VAGUS NERVE IN THE REGULATION OF AMOUNT OF ADIPOSE TISSUE

Vagus nerves may influence the formation of visceral adipose tissue. Rats subdiaphragmatic total vagotomy and vagal deafferentiation with capsaicin have shown that both efferent and afferent vagal neural pathways are involved in the development of diet-induced obesity, and both efferent and afferent vagal neural pathways influence abdominal visceral adiposity (reduced in visceral abdominal fat), with consequent implications for the risk of the development of metabolic syndrome and cardiovascular disease [37].

We proved in rats with long-term vagal stimulation decrease of epididymal fat pad weight, reflecting the total body fat content [34–36]. In our experiment we observed significant serum leptin level decrease after VNS, correlating with decreased weigh gain and reduction in food consumption [38, 36].

Banni et al. recorded that exposure of rats to VNS for 4 weeks reduced feed conversion efficiency as well as body weight gain (by aprox. 25%) and the amount of mesenteric adipose tissue (by approx. 45%) in comparison with those in sham-operated control animals [26].

The vagus nerve has a role in regulating weight by modulating visceral fat in humans. Miyato et al. described, measured in a computed tomography (CT) scans, decrease in visceral fat mass in 77 patients who had undergone gastrectomy due to early gastric cancer [39]. The reduction in visceral fat mass was significantly lower in vagus nerve-preserved than in vagus nerve-non-preserved cases. Reduction of the visceral fat, when the total fat tissue in these patients have been unchanged, is essential because this visceral fat is responsible for obesity results, more than mass of whole fat tissue of the body.

Kreier et al. reported that the intra-abdominal and subcutaneous fat pads in rats are innervated by separate parasympathetic neurons [40].

From these anatomical and physiological relationships there is a rationale for nervus vagus manipulation in attempt for obesity treatment in humans.

ELECTRICAL VAGUS NERVE STIMULATION IN HUMANS

Obesity is a serious medical problem, more serious and dangerous because we lack effective ways of treatment. There are different possibilities for heavy obesity treatment. Bariatric surgery is the most effective form of treatment, but application of this therapy is limited by its side effects, and only the most seriously obese are, therefore, typically treated with bariatric surgery. Implantable devices that stimulate, block, or modulate vagal nerve activity are a new, potential treatment developed for weight loss.

Vagus nerve stimulation (VNS) is a wide general term relating to many different techniques of vagus nerve excitation. In experiments on animals vagus nerve was approachable and stimulated through the abdomen cavity, mainly subdiaphragmatically. In case of almost all experiments in humans VNS relates to stimulation of left cervical VN with the use of commercial device VNS Therapy System.

WHY VAGUS NERVE STIMULATION IS USED IN OBESITY TREATMENT?

VNS seems to be logic solution because obesity is an energy imbalance regulated by CNS, and vagus nerve provides information from the periphery to the energy control center in the hypothalamus. VNS is safe and well-tolerated, safer than direct brain induction, and thus makes more attractive therapy option [41]. First treatment with VN stimulation has been applied in cats to stop epilepsy fit [42]. First VN stimulator in humans had been implanted in the year 1988 [43].

DATA FROM OBSERVATION MADE ON HUMANS WITH VAGUS NERVE STIMULATION

The role of vagus nerve part in body weight regulation can be traced since 1930 in works of Dragstedt, who established vagotomy as the cure for peptic ulcer surgical treatment. This evolving method of peptic ulcer disease treatment brought more scientific experiments leading to include vagotomy as the obesity treatment as well. Increasing popularity of vagotomy made many new important clinical and experimental facts. Kral underlined that vagotomy on its own, which undoubtedly improved glucose homeostasis in operated patients, lead to a wide range of weight loss [44, 45]. Gastric pacing as the method of morbid obesity treatment was proposed by Cigaina [46].

Vagotomy for weight loss, however, never gained much popularity due to concerns for motility side effects as well as greater weight loss achieved by the evolving gastric bypass operation [47].

First examinations with VNS in humans have not been carried on patients with obesity but with others illnesses. There is a clinical experience with VNS for epilepsy treatment. During VNS applied as an epilepsy treatment in some patients decrease in weight have been observed as a "side-effects" [48, 49]. After over 37 kg weight loss had been noticed in one patient with VNS Borneo at al. conducted a retrospective analysis of these data obtained from the group of 27 patients and have noted weight loss in 17 of them. Weight loss in patients according to Burneo may be due to decreased appetite, resulting in changes in eating behavior, or to gastrointestinal side effects, such as dyspepsia, previously reported as a side effect of VNS [49]. Weight loss was observed as side effect in part of people treated with VNS during pharmacologically resistant epilepsy or depression treatment [50].

Kansagra et al. in first retrospective study on children with long-term VNS applied in epileptic children have not noticed any changes in body mass index (BMI) during VNS [51].

Koren and Holmes in retrospective analysis of body weight changes in 21 patients with 2-year Cyberonics VNS Therapy System for epilepsy did not notice any body mass changes [52]. On the other hand Pardo at al. in 14 patients treated for drug resistant depression with VNS for over one year have reported significant, gradual weight loss despite the patients' report of not dieting or exercising [53]. The weight loss was proportional to the initial BMI, that is, the more severe the obesity, the greater the weight loss. Patients were using NCP Model 101 device, Cyberonics Inc., USA for stimulation of left vagus nerve in neck area in its neck location. The right vagus is not used typically because of greater vagal side effects at the heart or pulmonary level.

Camilleri et al. in experiments with human with mean body mass index (BMI) 39.3, sponsored by EnteroMedics Inc, using a laparoscopically implantable device to intermittent blockade of both subdiaphragmatic vagal nerves signaling with electrical pulses described effects VBLOC therapy (Vagal BLocking for Obesity Control) in obesity treatment [54, 55]. Implantable components were two flexible leads (including one electrode for each the anterior and posterior intra-abdominal vagal nerve trunks) that were connected to an implantable neuroregulator placed subcutaneously on the abdominal wall below the costal margin. Basing on his previous experimental work on pigs Camilleri set biphasic pulses at a frequency of 5000 Hz to block the neural impulses in the vagal trunks [56]. Both VN were stimulated for 90 seconds (first generation device) [54] or 120 seconds (second generator device) [55] periods with 5 minutes rest periods for 12 hours a day, from morning till evening. After six month of treatment body weight loss had been achieved, modest at 14.2% for first-generation device and 22.7% decrease of excessive body weight for second generation device. Excess body weight was defined as total body weight less ideal body weight. It is not known how to explain obtained body mass reduction after implanting VBLOC whether as

blockade of efferent or afferent impulsation in vagus nerve [57]. Possible changes of hormonal milieu have not been examined [57]. Recently published randomized, double-blinded, multicenter, controlled big trial of intermittent vagal blockade in subjects with morbid obesity to verify the VBLOC study, comes from fifteen laboratory centers in USA and Australia [58]. Experiments were sponsored by EnteroMedics Inc, St. Paul, MN. Results from one year observation were carried on 294 obese patients with BMI >41, with implanted devices, including 192 patients with implanted active/treated VBLOC and a group of 102 as non-treated control group. In summary, under the conditions of this EMPOWER study, authors were unable to demonstrate any difference in the treated and control groups in percent excess weight loss (EWL) [58]. 12-month percent EWL was 17 ± 2% for the treated and 16 ± 2 % for the control group.

VNS explains effect of acupunctural loosing weight in humans. Acupuncture stimulates auricular branch of vagus nerve. It is also responsible for the increase in serotonin (5-HT) level. Both changes lead to increased stomach smooth muscle tones, responsible for suppressing appetite [59].

WHAT SHOULD BE TAKEN INTO ACCOUNT DURING VAGUS NERVE STIMULATION? WHAT PROBLEMS OCCUR DURING VAGUS NERVE STIMULATION?

Constant current stimulation or constant voltage stimulation?

Val-Laillet et al. in an interesting work with chronic VNS on both vagus nerves in minipigs used bilateral vagal electrodes connected to constant current stimulators (2 mA, 30 Hz, 500-ms pulse, ON 30 s, OFF 5 min), while most authors used constant voltage stimulation because the circuitry is simpler than constant current stimulation [60]. Unfortunately, in a voltage control scheme an increase in resistance anywhere in the electrical conduction path will cause an additional voltage drop, decreasing the current at the nerve level and potentially causing it to be insufficient for stimulation [61]. Because the level of neuronal membrane depolarization is related to the applied current, the voltage but not current control scheme results in a reduction of reproducibility between experiments and along the time course of the inflammatory response occurring at the nerve-electrode junction [61].

Stimulation of one or both vagus nerves?

VNS of both nerves is more efficient, but bilateral stimulation is more invasive [33]. Frontal (left) one has a liver branch.

Afferent or efferent stimulation?

Different scientists admit that they stimulate mainly afferent part (fibres) of vagus nerve [62]. Afferent unmyelinated C-type fibres of the vagus nerve are more sensitive and easily stimulated.

One side VNS with vagotomy in opposite side?

Laskiewicz et al. showed that effects of both vagal nerves stimulation on final body weight and food intake was significantly more effective than only single nerve MC pacing in rats [33]. Sobocki et al. demonstrated that bilateral VNS is more effective than unilateral stimulation due to bilateral compensation [62].

Roslin and Kurian chose to investigate bilateral stimulation of the vagus nerve in dogs, because the right and left trunks have different distributions in the abdomen and the contribution of both could be essential [41].

Stimulation on what level?

On the abdominal level because on the neck level there are side effects described [49, 62].

Continuous or periodic stimulation?

Periodic better as chronic may lead to nerve damage [63].

IS VAGUS NERVE AN EFFICIENTLY STIMULATED INDEED? WHAT ARE THE METHODS TO VERIFY THE VAGUS NERVE STIMULATION?

VNS may induce nerve alternation, as described in review by Cohen and Georgievskaya [64]. There is a possibility of vagus nerve damage or its regeneration after vagotomy. For obvious reasons morphological and functional verification of VNS effectiveness is not conducted on humans. Not many authors verify effectiveness of VNS in experiments on animals for example intracellular recording in NTS or by c-Fos/c-fos searching. Most authors abandon such verification and explain it somehow, but majority of them do not mention such problem. But one has to remember that effective stimulation and transmission of induction are vital. Val-Laillet histologically controlled VN at the location of the stimulating electrodes, showing only one stimulated nerve with signs of inflammation [60]. Some authors verified effectiveness of VNS declaring increased c-Fos expression immunoreactivity in neurons of nodose ganglion of vagus nerve after chronic left vagus nerve stimulation [65, 66].

It is also very important to remember that vagus nerve can be killed during prolonged or not adequate stimulation. One has to remember not to damage vagus nerve. Possible vagus nerve damage during electrostimulation is discussed in the elegant work of Cohen and Georgievskaya [64].

CONCLUSION

Vagus nerve plays an important role in regulation of nutrient homeostasis and body weight. Many already discovered mechanisms in which vagus nerves took part had been used in several ways of treatment, and those newly discovered and not yet known may become targets in obesity treatment.

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