Journal of Diabetes Science and Technology
Volume 2, Issue 3, May 2008

Devices for the Treatment of Obesity: Will Understanding the Physiology of Satiety Unravel New Targets for Intervention?

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Abstract

The rise in the prevalence of obesity in the last few decades and its growing impact on health has driven the scientific community to investigate the physiological basis of energy homeostasis and mechanisms of satiety, and seek targets for intervention against this burgeoning epidemic. Recent findings highlight the role of gut-derived, hormonal signals in the regulation of satiety. These hormones act together with the dense and intricate enteric nervous system to coordinate and regulate gastrointestinal satiety signals, motility, and digestive processes. Bariatric surgical approaches attempt to take advantage of these mechanisms to facilitate early satiety and weight loss. Some of these procedures, by altering the anatomical structure of the upper gastrointestinal tract, also modify the hormonal response to food. Similarly, devices such as volume-occupying elements and nerve stimulators attempt to alter the gastrointestinal milieu in a manner that will ultimately lead to long-term weight loss. Novel surgical, endoscopic, and device-oriented methodologies seem to be promising approaches to treat obesity, yet further research is needed to appreciate their long-term effect.

J Diabetes Sci Technol 2008;2(3):501-508

Introduction

The obesity epidemic among adults and children in the developed and developing world poses a global threat that will have a major impact on population longevity as well as on health-related expenses.[1] The rise in the prevalence of obesity in the last few decades and its growing impact on health have driven the scientific community to investigate the physiological basis of energy homeostasis and seek targets for intervention against this burgeoning epidemic. In simple terms, long-term excess of energy intake in comparison with energy expenditure results in net energy excess manifested as weight gain. The regulation of both arms of the energy balance system involves multiple inputs from chemical, hormonal, neural, and environmental effectors, some of which have been known for decades while others have only recently been discovered. The increased research efforts in this fascinating area have led to the discovery of novel hormonal signals that constitute elements of the feedback loops governing energy balance, and of neuronal circuits that provide the central

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Abbreviations: (CCK) cholecystokinin, (CNS) central nervous system, (GI) gastrointestinal, (GLP-1) glucagon-like peptide-1, (IGLE) intraganglionic laminar ending, (IMA) intramuscular array, (IVA) intravillous arbor, (NOTES) natural orifice translumenal endoscopic surgery, (PYY3-36) peptide YY3-36

Keywords: bariatric surgery, device, gut hormones, obesity, visceral nerves

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nervous system (CNS) with cues regarding contents of the gastrointestinal (GI) tract and various energetic stores. The findings mentioned earlier have led to the identification of various attractive targets for intervention (pharmacological and nonpharmacological) that are designed to have an overall, long-term effect that will lead to a negative energy balance, i.e., greater energy expenditure in comparison to energy intake. This review will focus on potential *nonpharmacological approaches* to address the problem of obesity in view of the physiologic understanding of energy homeostasis. The main focus is on the energy intake arm of energy homeostasis, i.e., regulation of food consumption by affecting satiety. Obviously, increasing energy expenditure has a positive effect against obesity, and several pharmacological interventions have aimed at altering this component of the energy balance, which seems to be extremely difficult to achieve by straightforward recommendations (such as increasing physical activity). The present review will focus on the energy-intake arm of the balance and describe mechanisms that underlie the regulation of food intake and satiety.

Feedback Mechanisms in the Control of Food Intake

Food intake is controlled by several sets of mechanisms that vary in their time action profile. These feedback loops provide continuous cues to brain centers, where an integrative process determines overall energy expenditure and energy intake. "Satiety" is a series of events following the oral intake of food that affect the size and length of the present meal and the length of the interval until the next meal.[2] A major aim of the gastrointestinal signals provided by the gut is to optimize the digestive process of consumed nutrients.[3] This aim is achieved by a delicate balance between the coordinated motility of the system (affecting the transit time of food in various segments of the system), secretion of enzymes and other agents affecting the chemical digestive process, and termination of further consumption when the system reaches its capacity to perform efficiently and is exposed to the potential adverse effects of partially digested food in distal segments of the gut. The importance of gastrointestinal transit of food in modulating satiety is emphasized by the observation of Pavlov in the late 1800s that the draining of food from the upper gastrointestinal tract via an esophageal fistula resulted in persistent hyperphagia.[4]

The long-term controls include hormonal substances such as leptin, an adipocytokine secreted by adipose tissue as well as the stomach,[5,6] which serves as a long term signal reflecting available energy stores.[7] Elevated leptin levels act, among other brain loci, in the ventromedial hypothalamus by eventually affecting the melanocortin-4 receptor; they induce a sympathetic activation favoring energy expenditure and reduced further intake of food.[8,9] Mutations in the leptin gene or in leptin receptors induce a persistent state of polyphagia and result in marked obesity.[10] Medium-term feedback loops include multiple hormonal signals that vary throughout the day and in response to feeding, such as insulin and ghrelin.[11] While insulin rises following meals, ghrelin is elevated in fasting conditions and decreases in response to meals.[12] Both hormones, insulin by rising and ghrelin by decreasing, provide signals to satiety centers in the brain and induce a transition of the metabolic milieu to a state favoring sympathetic activation, increased energy expenditure, and reduced oral intake of food. The hormones and peptides providing satiety signals are secreted from multiple elements within the gastrointestinal tract. While hormones like peptide YY3-36 (PYY3-36) and ghrelin are secreted from cells within the intestinal and gastric mucosa, respectively, pancreatic polypeptide and amylin are secreted from the pancreas.[13] PYY3-36 has been shown to reduce food intake when administered exogenously.[14]

The short-term feedback loops provide the immediate information regarding meal size and content. These signals serve as the main determinants of an individual meal's length and termination. The signals participating in the short term feedback loop include the early changes in gut-derived hormones and direct neuronal activation in the gastrointestinal mucosa and wall, resulting from mechanical forces and direct contact with specific food constituents.[15] The neural elements of these feedback loops include the autonomic system nerve fibers that innervate the gastrointestinal mucosa and wall, known as visceral afferents. These afferents provide the CNS with inputs regarding immediate food and liquid consumption, digestive processes, and specific constituents of the digested matter.[16] While the long-term feedback loops govern the postabsorptive state and determine the handling of the consumed energy (storage vs consumption), the short- and medium-term feedback loops determine the immediate length of the meal by way of affecting the overall "satiety" of the individual. One cannot view the various feedback loops described herein as isolated elements, as they all interact with each other. Thus, some of the long- and medium-term hormonal signals such as leptin or insulin can act as modulators of the CNS responsivity to the vagal and hormonal signals from the gut.[17]

Recent discoveries have unraveled the dense and multilayered visceral afferent nervous system of the gastrointestinal tract that provides a rich array of mechanical-, nociceptive-, chemical-, and temperature-related signals to higher brain centers. The majority of short-term and direct controls of feeding are provided by vagal afferents that transmit and carry information regarding the chemical and mechanical properties of the consumed food.[18] The nuclei of the relevant vagal afferents are located in the nodose ganglion outside of the skull, and this has been used in order to inject the nuclei with tracer dyes and characterize their projections.[19] These studies revealed that the vagal afferents consist of various nerve endings with different receptor characteristics and with individual distribution. The first of these receptors characterized were intraganglionic laminar endings (IGLEs) which serve as mechanoreceptors that convert tension and shear forces from within the GI lumen into neural signaling aimed at coordinating the transport of food through the system.[20] IGLEs are found to be richly distributed throughout the whole GI system with a specifically high density in the corpus and antrum of the stomach. Another set of receptors are the intramuscular arrays (IMAs) that reside within the smooth muscle of the outer muscular layer of the upper GI wall and probably act as stretch receptors providing inputs regarding gastric distention.[21] IMAs have also been shown to be typically located in the stomach, specifically near the pylorus. The intravillous arbors (IVAs) typically innervate a small number of adjacent mucosal villi and probably serve as chemical receptors with high sophistication to specific chemical substances derived from ingested nutrients or from autocrine and paracrine signals from adjacent cells within the villous. The IVAs are found throughout the GI tract with a slightly larger density in the proximal small intestine.[22] Importantly, while the upper GI tract, namely the stomach and duodenum, seems to be the most highly innervated by dense networks of neurons, these constitute vagal as well as spinal projections. The interactions of these inputs provide central as well as local feedbacks to affect intestinal motility and satiety. A simplistic view of these feedbacks assumes that the stomach provides mechanical volume and tension-derived satiety signals, while the intestine provides nutritive satiety signals. Apparently, independently of their central effects, the gut-derived signals can affect the stomach directly by modifying the rate of gastric emptying by altering gastric mechanoreceptor sensitivity to stimulation.[23]

It is important to appreciate that despite the fact that multiple satiety signals originate from the gastrointestinal system and peripheral fat stores, including hormones and neural activation, the appetite centers in the brain receive multiple inputs from other CNS loci, and our feeding behavior is also affected by hedonistic effects as well as inputs from other higher centers.[24] This allows humans to "override" the multiple peripheral signals their energy balance and satiety centers receive, and maintain a behavior that seems to contradict and mismatch the seemingly anticipated response. Such behaviors include self starvation in conditions such as anorexia nervosa[25] and overeating in specific social circumstances or in events such as religious rituals.[26]

Strategies to Reduce Energy Intake

The traditional pharmaceutical approach aims at providing anorexogenic signals to the CNS by way of exogenously administrating hormones and peptides that increase satiety or their agonists, such as PYY3-36, or reducing the clearance of these hormones or peptides from the circulation.[27] Another option is to reduce or modify the absorption of nutrients from the gastrointestinal system by way of inhibition of the digestion of fats or carbohydrates. These approaches are under intensive investigation by multiple academic and industry researchers and have brought the first approved agents against obesity to the market: orlistat (a lipase inhibitor that reduce absorption of fat), sibutramine, and rimonabant (centrally acting agents affecting satiety centers directly).[28] The pharmacological approach, when combined with lifestyle modifications of diet and activity, provides a 5–10% weight loss over months of treatment that eventually reaches a plateau that can be maintained as long as the compound is still taken and the behavioral changes persist. The use of these agents can induce weight loss alongside improvements in the overall metabolic profile, yet is limited by side effects in certain patients.[29,30]

There have been several active strategies to limit oral consumption of food by using nonpharmaceutical approaches. These approaches include mechanical limitation of food consumption in the upper gastrointestinal tract, as well as anatomical modifications of the gastrointestinal tract achieved surgically, and attempts to provide neural and mechanical stimuli from the gastrointestinal tract to the CNS via the afferent autonomic fibers.

Surgical Modifications of the Gastrointestinal System

The most effective treatment of obesity to date is surgery. The various procedures result in a loss of excess weight

in the range of 40–75%, depending on the procedure performed.[31,32] More importantly, in some procedures, even before weight loss occurs, a significant improvement in metabolic risk factors such as altered glucose metabolism and dyslipidemia occurs. The surgical approach to the treatment of obesity attempts to combine anatomical and mechanical restriction of oral intake with alterations of the hormonal profile in response to food. In the past, jaw fixation was used to restrict oral intake of food in obese patients. Despite the fact that it did result in significant weight loss, this procedure was later abandoned due to the psychiatric side effects.[33] Present-day surgical procedures range from simple, adjustable gastric banding to larger-scale anatomical modifications such as the roux-and-Y gastric bypass. While gastric banding creates a reduced-size gastric pouch that limits the amount of food consumed per meal without changing the anatomical continuation of the gastrointestinal tract, the gastric bypass procedure combines the creation of a small gastric pouch with an anatomical diversion that bypasses the duodenum and a variable jejunal segment, resulting in an anastomosis of the gastric pouch and the jejunum. A third operation that has been used in the past is the biliopancreatic diversion procedure, where the stomach is restricted in size and the jejunal segment is anastomozed to the distal ileum. A modification of this procedure includes only the creation of a gastric sleeve without further alterations of the normal anatomy.[34] The restrictive element of these procedures, namely the restriction of the gastric contents, causes early satiety by way of distention of the pouch and lower esophagus.[35] The mechanism by which gastric distention causes this effect is by activation of mechanoreceptors in the gastric and esophageal wall.[36] In contrast to the adjustable band, in the gastric bypass procedure the restrictive element of the operation usually decreases over time as the pouch stretches, yet the exposure of the jejunum to food in the early phases of digestion is probably responsible to the hormonal effects of the procedure.[37] Indeed, following gastric bypass, ghrelin levels have been shown to decrease while PYY3-36 and glucagon-like peptide-1 (GLP-1) levels are increased following meals in patients who underwent this procedure.[38] Whether the observed hormonal changes are the result of the early exposure of various segments of the gut to nutrients and food elements, or to modifications of the autonomic neural network as a result from the surgical procedure, remains to be studied. The distance chosen for creating the anastomosis in the gastric bypass or biliopancreatic diversion procedures determines the magnitude of malabsorption created by these operations that adds a further component to the weight-loss effect.[39]

In the past, the bariatric operations were performed as a laparotomy, and these procedures were considered of significant surgical risk, especially as obese patients tend to have increased intrasurgical and postsurgical complications. In recent years, the vast majority of procedures are performed laparoscopically and the minimally-invasive technique has markedly reduced the risk of the procedure and the postsurgical period. Several investigators are aiming at further reducing the "invasiveness" of the procedure by attempting to perform restrictive gastric procedures endoscopically without penetration of the abdominal wall.[40] The novel NOTES (natural orifice translumenal endoscopic surgery) approach attempts to perform intraabdominal procedures by way of penetrating the stomach via an endoscope and may serve as another option for bariatric procedures such as gastroplasties. The obvious advantages of this approach are the lack of external surgical wounds and the shortened healing process. Preliminary human studies using this approach seem promising,[41] yet the amount of data is still limited.[42] As the results of gastric banding and sleeve gastrectomy seem to be promising with regards to weight loss (although the gastric sleeve, when not performed as part of a biliopancreatic diversion, has no long-term, follow-up data), it makes sense to perform isolated, gastric restrictive procedures without further modifications of the gastrointestinal anatomy. Importantly, performing such procedures from within the gastric lumen will probably have a smaller effect on the normal anatomy of visceral afferents in the gut wall.

While jaw fixation has been abandoned as an option to treat obesity, other more "user friendly" oral devices are still under development. Theoretically, any device that comfortably resides within the oral cavity and following food consumption causes an anatomical or other stimulation that will result in early cessation of the meal seems to be a logical and attractive approach. Such a device can limit jaw movement, similar to "jaw fixation," yet without the accompanying discomfort, thus resulting in smaller food portions consumed per bite and thus a longer eating period. As the various gut hormones that supposedly reduce oral intake respond to feeding within 20–30 minutes, slowing the eating process can result in an overall smaller meal due to activation of the medium-term, hormonal satiety signals.

Volume-Occupying Devices

Attempts to create an artificial restriction of gastric content by way of introducing an artificial bezoar have been under research and development in the last 30 years.[43]

As bezoars have been described in the medical literature since the early 20th century to have minimal symptoms except for weight loss, this approach seems feasible and attractive. A preliminary approach was to introduce a balloon, filled with air or fluid, into the stomach using an endoscope, inflating it within the stomach, and thus creating tension of the gastric wall and creating a restriction of oral intake due to the reduced remnant gastric volume. The problems encountered with such balloons were increased nausea and vomiting, and some isolated cases of perforation and escape of the balloon to the gut in the earlier versions. A 2007 Cochrane review of published data regarding the use of the intragastric balloon concluded that it was overall relatively safe, yet the benefits to weight loss were modest.[44] While this procedure can still be of benefit in severe obesity as an adjuvant to a low-calorie diet prior to a surgical procedure, it does not seem to be an appropriate option for mildly- and moderately-obese patients seeking weight loss.

Modification and Stimulation of Visceral Afferents

The discovery of the crucial role of visceral afferents in mediating meal termination and the growing amount of research into the gastrointestinal hormonal system and its role in the regulation of satiety attracted attempts to override the system by providing it with exogenous stimulation. The rationale behind these attempts seems straightforward and is to imitate the neural transmission to the CNS induced by intragastrointestinal mechanical forces and chemical stimuli by exogenous neural stimulation that will result in increased and earlier satiety[45,46] The obvious candidate for such manipulation is the vagus nerve, whose branches provide a dense network of neurons and their receptive fields in the upper gastrointestinal tract, namely the esophagus, stomach, and duodenum. Moreover, unlike the spinal afferents, the vagus has several large branches that can be visualized easily during a laproscopic procedure and be manipulated to be connected to external stimulation systems. Several attempts have been made by several groups to induce weight loss by providing external vagal stimulation. This approach views the nerve itself as a conducting cable that allows information flow from the gastrointestinal nerve endings in the form of electrical impulses to the CNS.[47] The original studies of direct vagal stimulation were performed in animals and demonstrated a weight reduction over an 8-week period in pigs.[48] The observed effects in that study were reduced weight in stimulated animals and reduced gastric emptying without overall reduction in food intake, emphasizing the potential central effects of vagal stimulation on overall energy homeostasis. The majority of researchers suggest that stimulation of the anterior vagal trunk is preferable due to the fact that it supplies the hepatic segment that transmits satiety inputs through exposure to glucose. There are published data on weight loss in humans following vagal stimulation that was indicated for treatment of epilepsy,[49] yet further studies are needed to evaluate the utility of this approach.

It is reasonable to assume that some of the success achieved by the surgical procedures described earlier is due to a modification of the short-term, visceral feedback loops, favoring inputs indicating satiety and early termination of meals. Possibly, the anatomical manipulations of the upper GI tract result in sensitization or lower thresholds of activation of visceral afferents by smaller amounts of consumed food, resulting in increased satiety leading to weight loss. Similarly, the early exposure of rather proximal segments of the small intestine to nutrients, as a result of the gastric bypass or the biliopancreatic diversion, may result in excessive discharge from chemosensitive visceral afferents, resulting in slower gastric passage and food, and increased secretion of gut-derived satiety signals, such as GLP-1 and PYY3-36.[50]

Modification of Gastric Motility

Gastric motility and wall tension have direct effects on the clearance of food from the stomach, as well as on satiety signals transmitted from this organ.[51] This led investigators to attempt to provide the stomach with an exogenous pacemaker, specifically at periods of meals, that would induce myoelectrical activity that would result in reduced gastric emptying, thus limiting food intake. In canine models, chronic gastric stimulation for 1 month resulted in a reduction in the rhythmicity and amplitude of the gastric slow waves following meals.[52] Similar results were later demonstrated in humans,[53] with a postprandial increase in tachygastria, an accelerated rhythm typically associated with reduced peristalsis of the stomach accompanied by symptoms of bloating and dyspepsia. Aside from modifying the intrinsic myoelectrical activity of the gastric walls, it also has a potential to affect gastric accommodation, i.e.. the relaxation process of the gastric walls that follows meal ingestion. The accommodation process represents the difference in the volume of the stomach between the fasting and the postprandial state. During the process of accommodation, gastric walls distend, thus activating mechanical receptors within

them, and motility propagates food outside of the stomach by way of coordinated peristalsis before gastric maximal capacity is reached. It is speculated that direct gastric stimulation results in reduced gastric wall tone, resulting in gastric distention and increased afferent discharge, leading to earlier satiety.[54] Furthermore, it is possible that direct gastric stimulation results in reduced antral contractions, leading to less effective peristalsis and slower evacuation of gastric contents.[55] In canines, chronic gastric stimulation has been shown to decrease vagal *efferent* discharge, shown by spectral analysis of heart rate variability, suggesting that the stimulation may tip the autonomic system balance to a more "sympathetic" predominance, favoring greater energy expenditure.

Future Prospects

The appreciation of the crucial role of visceral afferents in the short-term regulation of satiety and the broad array of receptors of these afferents highlight their role as potential targets for stimulation from within the gastrointestinal lumen. As described earlier, vagal and spinal afferents have multiple receptors that respond to mechanical, chemical (nutrient-derived), temperature, and paracrine stimuli. One can speculate that providing the stomach and duodenum with long-term stimuli that induce a response similar to the one resulting from food consumption, whether by mechanical, chemical, or pharmacological means, will result in increased afferent signaling to the CNS, leading to increased satiety. The problem of delivering such stimuli persistently by an intralumenal device is that any such device has to be resistant to the peristaltic forces of the gastrointestinal tract and maintain positioning within the anatomical region of interest, despite the continuous passage of food and mechanical forces applied from the walls. Attempts to create small, substance delivery reservoirs that can remain within the stomach and deliver specific chemicals to the pyloric region and duodenum are being actively pursued, but no clinical results are yet available. Delivery of selected nutrients that activate chemosensitive visceral afferents (such as specific fatty acids), or specific agonists of hormonal receptors on visceral receptors (such as cholecystokinin (CCK) agonists) imitating the paracrine effect of the local secretion of these hormones, may result in efficient and effective stimuli that will lead to increased satiety and reduced oral intake. Another option being actively explored is the transplantation of electrodes within the gastric lumen that provide electrical stimulation directly to the mucosa.[56] The high density of visceral afferents in the upper gastrointestinal tract, namely the stomach and duodenum, provides an attractive area for provision of "false" satiety signals or other stimuli that will sensitize the relevant visceral afferents to produce satiety signals at lower thresholds of activation or potentially reduce orexogenic signals originating from these afferents. It seems that attempting to override the vagal neural transmission by exogenous stimulation creates a nonselective activation of orexogenic and anorexogenic fibers that are within the stimulated nerve bundle and creates a signal that is difficult to predict. On the other hand, achieving a stimulation of visceral afferents that transmit signals that promote satiety without activating others will demand very high selectivity and accurate localization of such a stimulatory device.

Conclusions

Recent advances in the understanding of the central and peripheral mechanisms that regulate satiety and energy intake have promoted the identification of attractive targets for intervention against the burgeoning epidemic of obesity. Alongside the efforts in the pharmacological route, surgical- and device-oriented solutions may provide effective solutions for obese individuals. As some of the surgical interventions have proven their efficacy against obesity and related metabolic disorders, any approach that minimizes the "invasiveness" of the procedure and reduces the related surgical and postsurgical risks while providing similar efficacy, is a promising route to pursue. Furthermore, visceral afferents seem to be an extremely important and relevant target for the provision of stimulatory signals that will promote earlier termination of meals. The understanding of the anatomy, distribution, and different receptive characteristics of these afferents may help researchers to better understand their mechanism of action and design novel surgical interventions that will favor preservation of neural braches that transmit the more anorexogenic signals.

As the multiple feedback loops that regulate satiety and energy balance comprise a very complex system with multiple inputs from various sources alongside a broad set of efferent outputs, attempting to modify such a system may be reminiscent of the treatment of other complex physiological alterations such as hypertension or type 2 diabetes. In both cases, monotherapy aimed at a single component of the feedback systems usually works for a while, yet an addition of another drug aimed at a different element of the system is eventually needed. Similarly, it seems reasonable to assume that future successful treatment of obesity will include targeting more than one element involved in the regulation of

satiety. It has been demonstrated that some of the long-acting adiposity signals, such as leptin or insulin, may have a central[57] and peripheral[58] (on gut mucosa cells) sensitization effect on the central inputs and rate of secretion, respectively, of short-term peripheral satiety signals such as CCK or GLP-1, emphasizing that targeting more than one component of the feedback loops may have a synergistic effect. Such combinations may be comprised of multiple pharmaceutical agents, a combination of a device and a drug, or even a device that simultaneously targets more than one component of the system. As mentioned earlier, even when all inputs are promoting a state of satiety, other higher brain centers may still promote a behavior of continued food consumption for hedonistic or other reasons. This point should be emphasized, as any successful treatment for obesity that will be maintained over time should include a behavior-modification component that strengthens positive eating habits, a healthy diet, and increased physical activity.

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