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The vagus nerve, food intake and obesity

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Abstract

Food interacts with sensors all along the alimentary canal to provide the brain with information regarding its composition, energy content, and beneficial effect. Vagal afferents innervating the gastrointestinal tract, pancreas, and liver provide a rapid and discrete account of digestible food in the alimentary canal, as well as circulating and stored fuels, while vagal efferents together with the sympathetic nervous system and hormonal mechanisms codetermine the rate of nutrient absorption, partitioning, storage, and mobilization. Although vagal sensory mechanisms play a crucial role in the neural mechanism of satiation, there is little evidence suggesting a significant role in long-term energy homeostasis. However, increasing recognition of vagal involvement in the putative mechanisms making bariatric surgeries the most effective treatment for obesity should greatly stimulate future research to uncover the many details regarding the specific transduction mechanisms in the periphery and the inter-and intra-neuronal signaling cascades disseminating vagal information across the neuraxis.

Keywords

Gut-brain axis; gut hormones; vagal afferents; obesity surgery; Roux-en-Y; gastric pacing

1. Ingested food interacts with sensors along the alimentary canal: importance of vagal afferents

1.1. Oral cavity: taste receptors and trigeminal mechanosensors

Gustatory input via taste receptor cells on the tongue and palate is considered most important for guiding food intake and selection (Fig. 1). Although only a minor portion of this information is mediated to the brain by the vagus nerve, the gustatory system is included here because it shares the nucleus tractus solitarius (NTS) and other central processing stations with vagal afferents from the gastrointestinal tract. The gustatory and trigeminal systems act as “gate keepers” at the entrance to the alimentary canal (Scott and Verhagen, 2000). According to this view, the classical four taste modalities represent innate detectors for acceptable foods (sweet), dangerous or toxic foods (bitter and sour), and special needs (salt, water).

There was considerable recent progress in taste receptor physiology, with a number of receptor proteins and signaling mechanisms discovered (as reviewed by (Sugita, 2006)). There is also some progress in deciphering the neural encoding mechanism. The observation that in the

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mouse, each taste bud is innervated by about 5 primary afferent geniculate ganglion cells that only innervate that bud, suggests a labeled-line system, although each taste bud can contain receptor cells of different modality (Zaidi and Whitehead, 2006). In addition to receptors for sweet, bitter, sour, and salty substances, there may also be a taste for fat. The fatty acid transporter CD36 is co-expressed with α-gustducin in taste receptor cells and unlike wildtype mice, CD36-deficient mice are unable to develop a preference for fatty foods (Laugerette et al., 2005). The newly discovered tastes for fat and amino acids (Umami) suggest that the system may be capable of at least recognizing, if not metering, the macronutrient content of mixed foods.

The trigeminal somatosensory system with its mechano- and temperature sensors picks up important additional attributes of ingested foods, such as creaminess and crunchiness. These are thought as important dimensions of overall palatability of particular food items.

Understanding the transduction mechanisms of the gustatory system may have important implications for investigation of chemosensory processes in the small intestines as discussed below.

1.2. Stomach: stretch, tension, leptin, and ghrelin

Far from being a passive reservoir for ingested food, the stomach is a highly regulated organ with elaborate neural and hormonal control mechanisms. The presence of ingested food is detected by vagal afferent fibers in the mucosa sensitive to mechanical touch (Berthoud et al., 2001), and the volume of ingested food is detected by vagal afferents in the external muscle layers sensitive to stretch and tension (Phillips and Powley, 2000) (Fig. 2). Intraganglionic laminar vagal afferent endings are located in the connective tissue capsule of myenteric plexus ganglia, between the longitudinal (outer) and circular (inner) muscle layers (Berthoud and Neuhuber, 2000). They thus respond to muscle tension generated by both passive stretch and active contraction of the muscle layers (Zagorodnyuk et al., 2001). This type of vagal afferent ending is found in large numbers throughout the esophagus and gastrointestinal tract (Berthoud et al., 1997; Neuhuber et al., 1998). Intramuscular arrays are distinctly different from intraganglionic laminar endings and are almost exclusively located in the stomach longitudinal and circular muscle layers (Berthoud and Powley, 1992) (Fig. 2). Although IMAs were thought to represent in-series tension receptors long before the functional proof of mechanosensitivity for IGLEs (Zagorodnyuk et al., 2001), it is now unclear how they are functionally different from IGLEs.

Vagal afferent fibers are also innervating the gastric mucosa, where they are likely to detect locally released hormones such as leptin and ghrelin. Leptin is produced in the mucosa of the stomach and rapidly mobilized by feeding and high doses of exogenous cholecystokinin (Bado et al., 1998), and it appears to activate vagal afferents (Wang et al., 1997), shown to express the long form of leptin receptor (Buyse et al., 2001; Burdyga et al., 2002). Small doses of leptin infused into the celiac artery significantly decreased sucrose intake and this effect was not observed in rats with subdiaphragmatic vagotomy or perivagal capsaicin-treatment aimed to selectively ablate vagal afferent fibers. It is unlikely that celiac artery leptin produced its effect by spilling into the systemic circulation because infusion of the same dose of leptin into the jugular vein did not reduce sucrose intake, and because the increases in circulating leptin were similar for both routes of infusion (Peters et al., 2006).

The very recent discovery of ghrelin was particularly exciting because it is the first and only peripherally secreted hormone with a stimulatory effect on appetite. Ghrelin is mainly secreted from oxyntic gland cells in the mucosa of the empty stomach and secretion is rapidly suppressed upon the ingestion of food (Cummings et al., 2001; Cummings, 2006). There is evidence from one laboratory that ghrelin secreted from the gastric mucosa stimulates appetite by inhibiting

activity of vagal afferents. Ghrelin's appetite-stimulating effect was abolished in rats with subdiaphragmatic vagotomy and in rats with capsaicin-induced vagal deafferentation (Date et al., 2002). Ghrelin receptor is expressed by a subset of vagal afferent neurons in the nodose ganglia and appears to regulate expression of other peptide receptors in vagal afferents (Date et al., 2002; Burdyga et al., 2006). Furthermore, ghrelin does not stimulate food intake in patients with surgical procedures involving vagotomy (le Roux et al., 2005).

Thus, besides mechanosensory signals, the stomach appears to generate hormonal signals that are picked up by vagal afferents. This is interesting with regard to the question whether the stomach can sense only food volume or energy as well. Available behavioral data using pyloric cuffs suggest that gastric satiation is strictly volumetric and intestinal satiation is nutritive (Powley and Phillips, 2004). The finding that the two gastric hormones leptin and ghrelin can modulate appetite and satiation puts an interesting twist to this view. While the nutrient sensors responsible for the release appear to be located in the small intestine, the hormone producing cells themselves are located in the stomach.

1.3. Upper small intestine: CCK, GIP, and "taste in the gut"

Vagal afferent innervation of the duodenal mucosa was demonstrated anatomically using DiI tracing from the rat nodose ganglia (Berthoud et al., 1995; Williams et al., 1997) (Fig. 2). Labeled vagal afferent fibers were present in the lamina propria of duodenal and jejunal villi and crypts of Lieberkühn, but do not cross the basal membrane to innervate the epithelial layer. Thus, vagal afferents are not in a position to sense luminal nutrients directly. Double labeling with an antibody to CCK revealed the presence of close anatomical appositions between labeled vagal afferent fibers and CCK-ir enteroendocrine cells in the lamina propria of duodenum and jejunum (Berthoud and Patterson, 1996). Together with the demonstration that vagal afferents express CCK-1 receptor (Moriarty et al., 1997; Broberger et al., 1999; Patterson et al., 2002) and numerous functional studies, these findings strongly suggest that luminal nutrients, particularly lipids and proteins activate vagal afferents via release of CCK from adjacent enteroendocrine cells (Smith et al., 1985; Geary, 2004; Raybould et al., 2006).

Since glucose is a very poor stimulator of CCK release, it is not clear whether a similar mechanism exists for the sensing of glucose by vagal afferents. There is some limited evidence that 5-HT-secreting enteroendocrine cells and the 5-HT3 receptor might be involved (Freeman et al., 2006). The 5-HT3 receptor is expressed in vagal afferent neurons (Morales and Wang, 2002), and stimulation of c-Fos in nodose ganglion neurons by luminal administration of 5-HT or maltose was blocked by prior vagotomy or 5-HT3 receptor antagonist treatment (Wu et al., 2005).

Glucose-dependent Insulinotropic Polypeptide (GIP) also known as Gastric Inhibitory Polypeptide is secreted from K-cells primarily concentrated in the upper portions of the small intestine (Buchan et al., 1982). It is secreted in response to glucose ingestion and stimulates insulin secretion preferentially at high circulating glucose levels (Pederson et al., 1975; Andersen et al., 1978). Therefore, the GIP-cell can detect luminal glucose and could theoretically participate in the encoding of glucose-specific information to be transmitted to the brain. However, there is no evidence of receptors for this peptide on vagal afferent fibers and they are not activated by GIP (Nishizawa et al., 1996; Nakagawa et al., 2004). Furthermore, GIP release does not seem to be affected by vagotomy, direct efferent vagal stimulation, or indirect vagal stimulation through sham feeding (Berthoud et al., 1982; Ohneda et al., 1985).

Compared to the gustatory system, little is known about the encoding of nutritional information in the gut mucosa by enteroendocrine cells, primary afferent neurons of the enteric nervous system, and vagal afferents (Raybould, 2002). Some similarities are consistent with the possibility that the two systems evolved from a common precursor. One of the specialized cell

types in mammalian gastrointestinal mucosa, the brush cell (also known as tufted or caveolated cell), shares distinct features with the chemosensory taste receptor cells of the tongue. They both have an apical tuft of microvilli and express α-gustducin, the α subunit of the heterotrimeric cGMP-coupled protein involved in bitter transduction in oral taste receptor cells (Hofer et al., 1999; Rozengurt, 2006). Furthermore they all share the NTS as the first central relay and place of integration.

1.4. Lower gut: The ileal brake hormones GLP-1 and PYY

Polypeptide YY and Glucagon-like peptide 1, two peptide hormones secreted mainly from the lower gut, particularly the ileum, colon, and rectum, seem to be most relevant for the control of appetite. Interestingly they are both secreted from the same enteroendocrine cells, the L-cells. Because only high concentrations of glucose and fatty acids directly infused into the vascularly perfused rat ileum where effective in stimulating PYY secretion, it is thought that this mechanism represents the so called ileal brake, that operates only in cases of malabsorption or maldigestion (Dumoulin et al., 1998). However, since hydrolyzed protein was even more potent in stimulating PYY release from the perfused rat ileum (Dumoulin et al., 1998), and compared to high fat and high carbohydrate diets, high protein diet produced the highest PYY plasma levels (Batterham et al., 2006), it is possible that digested protein levels in the distal small intestine are high enough to physiologically stimulate PYY release.

In addition to direct stimulation by local luminal contents, the PYY producing L-cells appear to be stimulated also indirectly through a neural mechanism originating in the proximal gut and depend on intact vagal afferents, because peak PYY secretion is reached long before a meal has reached the PYY-rich part of the ileum and is blunted by tetrodotoxin, hexamethonium, and sensory vagotomy (Fu-Cheng et al., 1997). It is not clear whether this neural pathway is contained entirely within the myenteric plexus of the enteric nervous system or uses an extrinsic route via vago-vagal and/or vago-spinal reflexes.

Once PYY is released into the circulation, the first two amino acids are rapidly cleaved by dipeptidyl peptidase IV, resulting in $PYY_{3–36}$ (Eberlein et al., 1989). This truncated peptide has a high affinity for the Y2 receptor and has anorexigenic potency in both rats and humans (Larhammar, 1996; Batterham et al., 2002; Chelikani et al., 2005a; Batterham et al., 2006; Chelikani et al., 2006), whilst $PYY_{1–36}$ has a higher affinity for the Y1 and Y5 receptors and is orexigenic if injected into the brain. A physiological role for PYY in satiation is supported by the observation that PYY null mice are slightly hyperphagic and develop obesity, both effects being reversible with PYY3-36 administration (Batterham et al., 2006). PYY thereby appears to selectively affect the satiating effects of proteins but not fats and carbohydrates (Batterham et al., 2006).

Because $PYY_{3–36}$ can easily cross the blood brain barrier, and direct application of $PYY_{3–36}$ to neurons in the arcuate nucleus inhibits their activity, it has been suggested that the anorectic effect of peripheral $PYY_{3–36}$ is mediated by Y2 receptors in the arcuate nucleus (Batterham et al., 2002). However, vagal afferents may also be involved in the anorectic effects of $PYY_{3–36}$, as abdominal vagotomy abolished both the anorectic effect and c-Fos expression in the arcuate nucleus following peripherally administered $PYY_{3–36}$ (Koda et al., 2005). The Y2 receptor is expressed in at least some vagal afferents (Ghilardi et al., 1994; Zhang et al., 1997; Koda et al., 2005) and PYY stimulates firing of gastric vagal afferents (Koda et al., 2005).

Glucagon-like peptide-1 (GLP-1), also secreted from L-cells, is the site-specific splice product of the proglucagon gene also expressed in pancreatic islet cells where its major cleavage product is glucagon. Not unlike PYY, GLP-1 release also appears to be stimulated by all three macronutrients by both an indirect, partly neural reflex originating in the upper small intestine

and by direct mucosal contact in the lower gut (Herrmann-Rinke et al., 1995; Herrmann et al., 1995; Anini et al., 2002). GLP-1 actions on pancreatic hormone secretion and gastric emptying make it a powerful regulator of glycemic homeostasis (D'Alessio et al., 1995; Ritzel et al., 1995; Schirra and Goke, 2005).

Peripheral administration of GLP-1 or its stable analog exendin-4, the naturally occurring peptide from the Gila monster lizard, enhance satiation and reduce food intake in humans and rats (Gutzwiller et al., 1999; Chelikani et al., 2005b). Because of rapid breakdown by dipeptidyl peptidase-VI, endogenously secreted GLP-1 has a very short half-life in plasma. Thus, although endogenous GLP-1 may partly act as a true hormone through the circulation on feeding circuits in the brain, it could also act in a paracrine fashion on vagal afferent nerve fibers within the gut mucosa. This view is supported by observations that GLP-1 receptor is expressed in nodose ganglion and GLP-1 increases cytosolic Ca^{2+} and evokes action potentials in vagal afferent neurons (Kakei et al., 2002; Nakagawa et al., 2004). In addition, GLP-1 released from the ileum can also act through GLP-1 receptors expressed in the area postrema (Merchenthaler et al., 1999; Yamamoto et al., 2003) to activate catecholaminergic neurons with projections to the NTS, ventrolateral medulla, and parabrachial nucleus (Yamamoto et al., 2003). Studying the site of action for the anorectic action of GLP-1 is complicated by the fact that the peptide is also expressed in a small population of neurons in the NTS with projections to the hypothalamus (Tang-Christensen et al., 2001).

In summary, vagal afferent nerve fibers in the gastrointestinal tract are in an excellent position to pick up information regarding volume and composition of luminal contents. They can directly detect mechanical touch, distension, and stretch at any location. In addition, they can indirectly detect the presence and concentration of all three macronutrients through mediation by peptides and transmitters released from specialized endothelial cells. These peptides are also absorbed into the blood stream and can interact with receptors in specialized brain areas. There are still many unsolved issues regarding nutrition-related gut-to-brain communication. The relative contributions of the hormonal versus the paracrine, vagally mediated mode of action, to the control of satiation and appetite, as well as reflex control of gastrointestinal, pancreatic, and hepatic functions are uncertain. The relationship between individual vagal primary afferent neurons and the various populations of peptide-secreting enteroendocrine cells is ill defined.

2. Vagal and other autonomic hindbrain mechanisms involved in food intake and energy expenditure

2.1. Integration of vagal mechanisms within the hindbrain

The brainstem harbors an impressive array of neurons and circuits directly involved in ingestion, digestion, and absorption of food, as well as in utilization of metabolites and fuels. The neural circuits controlling most of these tasks are contained within the brainstem and do not require the forebrain for their execution. Just as for respiration and circulation, other body functions essential for survival, the regulation of nutrient supply is to a large extent autonomically organized within the brainstem.

The caudal brainstem contains the complete pathways necessary for mastication and swallowing, with all the accompanying autonomic responses such as saliva secretion (Jordan et al., 1992). Both mastication and deglutition are complex behaviors that involve cooperation between large numbers of muscles. Protection of the airways is of critical importance, so that certain muscles cannot be activated independently. Rhythmic, temporally fixed, and sequential patterns of muscle action are therefore organized within specialized pattern generator circuits.

Both the sensory and motor limbs of brainstem reflexes related to ingestion have been relatively well characterized because of easily available methodology such as anterograde and retrograde neuronal tracing and recording from nerve fibers (Fig. 3). However, it is much less understood how sensory information is processed and leads to meaningful motor action, as this analysis typically requires more challenging methodology. It should also be noted that gastrointestinal hormones released into the circulation could affect brainstem function independent of primary afferent nerves by acting directly on neurons in the area postrema and NTS. Both these structures have a weak or absent blood brain barrier (Gross et al., 1990) (Gross et al., 1991). Since dendrites of vagal motor neurons penetrate deep into the NTS, they could also be directly affected by circulating factors.

Based on experiments with the decerebrate rat, it appears that the isolated brainstem can terminate a meal and thus exhibit the basic behavior of satiety (for reviews see (Grill and Kaplan, 1990, 2002). This brainstem-based satiation process likely involves the activation of neurochemically specific NTS neurons such as the A2 catecholaminergic neurons (Rinaman et al., 1995; Rinaman, 2003), GLP-1 expressing neurons (Vrang et al., 2003)(ref), and POMC-expressing neurons in the commissural NTS (Fan et al., 2004).

Other areas in the hindbrain harbor sympathetic premotor neurons that ultimately control different steps involved in energy expenditure. These include neurons in the ventrolateral medulla and in the NTS innervating white adipose tissue responsible for fat mobilization (Bamshad et al., 1998; Bartness and Bamshad, 1998; Bamshad et al., 1999; Shi and Bartness, 2001) and neurons in the caudal raphé nuclei innervating brown adipose tissue responsible for thermogenesis (Morrison, 2001, 2003).

2.2. Integration of vagal mechanisms in the forebrain

The hypothalamic “center” hypothesis has dominated research on food intake during much of the last century. However, with the advent of neuronal tracing in the seventies, it became clear that the hypothalamus is well connected to most other areas of the brain and does not work in isolation. One of the emerging new views is that the neural system regulating energy balance is complex and distributed, involving specific areas of hindbrain, midbrain, and forebrain (Watts, 2000; Berthoud, 2002; Grill and Kaplan, 2002). Information from vagal sensors in the periphery arriving at the NTS is distributed widely in the CNS, including hypothalamus, amygdala, and cortex (Fig. 3). Some of these projections are direct, while others are indirect, via relay stations in the ventrolateral medulla, locus coeruleus, and parabrachial nucleus. There are particularly prominent direct ascending projections from the NTS to the paraventricular nucleus and weaker ones to the lateral hypothalamus and the dorsomedial and arcuate nuclei (Ricardo and Koh, 1978; Ter Horst et al., 1989; Cunningham et al., 1990). Thus, information from vagal afferents can be integrated with other nutritional information, as well as information pertaining to the time of day, reproductive cycle and state of arousal, all represented in the hypothalamus.

There is also ample anatomical and functional evidence for prominent descending projections from the hypothalamus to areas in the dorsal vagal complex and other feeding relevant areas in the caudal brainstem (Fig. 3). Hypothalamic neurons expressing the following peptides involved in food intake all project directly to the dorsal vagal complex and other brainstem areas: POMC/CART (Palkovits et al., 1987;Alessi et al., 1988), AGRP/NPY (Bagnol et al., 1999), oxytocin (Siaud et al., 1989;Rinaman, 1998), gastrin-releasing peptide (Bombesin) (Costello et al., 1991), orexin/dynorphin (Peyron et al., 1998), and MCH (Bittencourt et al., 1992). While AGRP, oxytocin, and MCH are exclusively expressed in the hypothalamus, POMC, NPY, and GRP are also expressed in the medulla (Joseph et al., 1985;Bronstein et al., 1992;Tohyama, 1998), and orexin is expressed in vagal afferent neurons (Kirchgessner,

2002). In addition, receptors for all these peptides have been identified in the dorsal vagal complex (Tohyama, 1998;Kishi et al., 2003).

There is also electrophysiological evidence suggesting that specific neurons in the dorsal vagal complex can be modulated by hypothalamic signals. Bereiter and coworkers (Bereiter et al., 1980) were the first to demonstrate that NTS neurons receiving oral input through the chorda tympany nerve are modulated by lateral hypothalamic stimulation. Such facilitation of gustatory responses in NTS neurons by lateral hypothalamic stimulation was recently confirmed in the hamster (Cho et al., 2002). Rogers and coworkers then demonstrated a similar effect of paraventricular nucleus stimulation on the activity of NTS neurons receiving gastrointestinal afferents through the vagus nerve (Rogers and Hermann, 1985). Most recently, Schwartz and Moran demonstrated opposing modulatory effects of intracerebroventricularly injected leptin and NPY on the electrical responsiveness of NTS neurons to gastric distension. Leptin increased distension-induced spike activity, whereas NPY decreased this activity (Schwartz and Moran, 2002). This study suggests that these peptides act at the level of the hypothalamus and via descending projections, but a direct action on the medulla cannot be excluded.

Finally, behavioral and functional evidence suggests that information from the hypothalamus can modulate the capacity of vagal satiety signals at the level of the dorsal vagal complex. Smith's proposal (Smith, 1996) for a new classification of the factors controlling meal size was an important stimulus for studies addressing the integration of short-term signals such as CCK (direct controls), and longer-term signals such as leptin (indirect controls). He defined food stimuli contacting preabsorptive receptors along the surface of the gut from the tip of the tongue to the end of the small intestine as direct controls and everything else as indirect controls. Indirect controls that require the forebrain (metabolic, ecologic and rhythmic), change meal size by modulating the potency of direct controls.

Smith's thesis was tested mainly by using c-Fos expression as an indicator of neural activity (Emond et al., 1999; Emond et al., 2001), analysis of food intake (McMinn et al., 2000; Matson et al., 2002) and meal structure (Eckel et al., 1998; Flynn et al., 1998; Schwartz et al., 1999; Azzara et al., 2002). The results of most of these studies show that leptin increases the potency of CCK to reduce meal size, supporting Smith's hypothesis. The behavioral effects where also reflected by changes in c-Fos expression in the NTS/area postrema (and hypothalamus).

Behavioral tests of the Smith hypothesis focused mainly on potential modulation of satiation by descending melanocortin projections. Williams et al. reported that the MC4/3 receptor agonist MTII decreased, and the antagonist SHU9119 increased food intake when injected directly into the dorsal vagal complex at doses subthreshold for 4^{th}-ventricular injections (Williams et al., 2000). Our own observations confirmed and extended these observations by demonstrating that DVC infusion of SHU9119 increases food intake by selectively increasing meal size, while not changing meal frequency. Also, with any exogenous injections, it is not clear whether the implicated endogenous ligand (α-MSH), originates from descending projections or local neurons, because POMC/α-MSH is expressed in a small population of neurons in the commissural NTS (Pilcher and Joseph, 1986; Palkovits et al., 1987; Bronstein et al., 1992) (Fig. 3).

3. The vagus and obesity

3.1. Evidence for vagal afferents in short- but not long-term control of food intake

Given this impressive breadth of sensory capacities of vagal afferents, one could expect that they play a crucial role in the control of food intake and possibly energy balance. Since vagal afferents transmit predominantly satiety signals from the gut to the brain, they seem important

for keeping appetite under control and may help prevent development of obesity. However, total food intake and body weight are surprisingly impervious to manipulations of vagal integrity. Total abdominal vagotomies or selective vagal de-afferentations do not cause hyperphagia and obesity, and electrical stimulation of vagal afferents does not appear to decrease food intake and body weight (Koren and Holmes, 2006). Vagal deafferentations do produce subtle increases in meal size (Schwartz et al., 1999; Kelly et al., 2000; Powley et al., 2005), but because there is partial compensation by more frequent meals, it does not result in excessive body weight gain. From these observations it would appear that, compared to systems in the hypothalamus, vagal afferents play only a secondary role in the control of long-term food intake and energy balance. However, the methodology used to manipulate vagal afferents is rudimentary at best, as they do not allow selective ablation or stimulation of functionally specific neurons. For example, given that ghrelin (Date et al., 2002) and hyperglycemia (Niijima, 1982) can suppress, while gastric distension and CCK (Schwartz et al., 1993) can increase firing activity of specific populations of vagal afferents, simply cutting or stimulating both populations should theoretically lead to cancellation of their central effects. By learning more about the functional specificity of vagal afferents and the availability of more selective tools to manipulate them, they are still a worthwhile target for prevention or treatment of obesity. This view is enforced by emerging evidence that the impressive efficiency of bariatric surgery may, at least in part, be related to changes in gastrointestinal hormones acting on vagal afferents.

3.2. Vagal mechanisms affected by obesity surgeries

Bariatric surgery is currently the most effective treatment for morbid obesity and the number of procedures has dramatically increased over the last 10 years. The older malabsorptive jejunoileal bypass and the simple restrictive operations such as vertical and adjustable gastric banding techniques have been largely abandoned because they had either serious side effects and/or poor long-term efficacy. They have now been almost completely replaced by the more effective Roux en Y gastric bypass surgery (RYGB)(Cummings et al., 2004). This surgery consists of a small pouch of about 5% of the most proximal stomach, which is anastomosed with the upper end of the cut proximal to mid-jejunum (Fig. 4). The lower end of the cut jejunum is re-anastomosed to the distal jejunum. The result is a nutrient limb consisting of the small gastric pouch and the distal ileum, a bilio-pancreatic diversion limb consisting of the large stomach remnant, duodenum, and proximal jejunum, and a common piece consisting of mainly the ileum and all of the large intestines. Although this procedure results in approximately 1% mortality rate, it is reported as highly efficient for extended periods of time in reducing food intake, body weight, and indices of type-2 diabetes (Trostler et al., 1995; MacDonald et al., 1997).

With respect to gut innervation, both the ventral and dorsal gastric branches of the vagus nerve on the large gastric remnant are cut by the gastrostomy procedure (Fig. 4). Because some of these branches, traveling along the lesser curvature also cross the pyloric sphincter and reach the proximal duodenum and parts of the pancreas (Stavney et al., 1963;Berthoud et al., 1990;Berthoud and Powley, 1990;Berthoud et al., 1991b;Kressel et al., 1994), these areas are also partially vagotomized after RYGB surgery. Both vagal preganglionic efferent and afferent fibers are affected. As postganglionic sympathetic fibers and dorsal root afferents also innervate the stomach mainly via the left gastric artery entering the stomach near the cardia, they are likewise interrupted after RYGB.

In contrast, some vagal and sympathetic innervation of the distal part of the antrum, the pylorus, proximal duodenum, and pancreas should remain intact, as they are supplied by the gastroduodenal branch originating from the ventral trunk and traveling along the same named artery (Berthoud et al., 1991a; Berthoud et al., 2004). Similarly, the two celiac vagal branches

traveling with the superior mesenteric artery and its subsidiaries and supplying most of the small and large intestines from the distal duodenum on downwards should remain intact. Special care has to be taken not to damage the dorsal celiac branch when carrying out the gastrostomy, as it exits the dorsal trunk very close to the gastric cardia. It would be helpful to carefully document the exact damage to nerves and to compare it with the outcome of each operation.

The other transection of nerve fibers in RYGB is associated with transection of the jejunum and affects mainly the enteric nervous system. Although this seems to have little impact on gut function, it may play some role in the communication between duodenal GIP and ileal GLP-1 secreting cells (Rocca and Brubaker, 1999), and may interrupt the migrating motor complex and normal peristalsis (Otterson and Sarr, 1993).

The potential mechanisms of hypophagia and weight loss have been discussed in an excellent review (Cummings et al., 2004). The most plausible explanation is reduced meal size because of the small capacity and accommodation of the gastric pouch. However, subjects could be expected to compensate for the smaller meal size by increasing meal frequency, and switching to energy dense foods, as has been seen after gastric banding. Two additional changes in RYGB patients, reduced ghrelin and increased PYY/GLP-1 secretion may prevent such compensatory behavior. Cummings and colleagues had hypothesized that ghrelin cells in the gastric mucosa may eventually cease to secrete ghrelin, as they are constantly stimulated by an empty stomach (override inhibition hypothesis) (Cummings et al., 2004). However, some doubt is cast on this explanation by reports of unchanged (Stoeckli et al., 2004), or even increased (Holdstock et al., 2003) ghrelin levels after RYGB, and by the observation in rats, that postprandial ghrelin suppression does not depend on nutrients in the stomach, but on nutrients in the duodenum and proximal jejunum (Williams et al., 2003a). Reflux of nutrients from the bypass limb into the proximal jejunum could thus still trigger prandial ghrelin suppression, rendering the override inhibition hypothesis doubtful.

As suggested by Cummings (Cummings et al., 2004), ghrelin secretion may be decreased after RYGB because of denervation of autonomic input to ghrelin cells in the stomach. Clearly, the entire gastric remnant containing most ghrelin cells is almost completely vagotomized and sympathectomized as discussed above (Fig. 4). Preliminary studies showed smaller fasting-induced increases of plasma ghrelin in subdiaphragmatic vagotomized rats, and an acute suppression with atropine treatment in intact rats (Williams et al., 2003b), suggesting that vagal efferents may be involved in the tonic increase of ghrelin in the empty stomach. However, more selective vagotomies, both in terms of vagal branches supplying specific targets and separating afferents from efferents, as well as vagal stimulation studies of the vascularly perfused stomach will be necessary to shed more light on the mechanisms involved. The need for more mechanistic studies is also indicated by disparate findings regarding vagal involvement of prandial ghrelin suppression. While in humans, vagal stimulation by means of modified sham feeding was able to enhance ghrelin suppression by oral fat intake (Heath et al., 2004) vagotomy was without any effect on basal levels or on re-feeding-induced suppression of ghrelin in rats (Williams et al., 2003b).

In light of the recent finding that electrical stimulation of sympathetic nerves supplying the upper abdominal viscera increases ghrelin concentration in portal blood, it is possible that the sympathetic nervous system may be more involved in the ghrelin spike during meal anticipation than the vagal system (Mundinger et al., 2006), and the complete sympathetic denervation of the stomach after RYGB surgery might explain low ghrelin levels observed by some. However, studies using a vascularly perfused stomach will be necessary to rule out indirect mediation of sympathetic stimulation-induced ghrelin secretion by other innervated targets in the stomach and adjacent organs.

Thus, lack of ghrelin secretion remains an attractive explanation for the success of RYGB in decreasing food intake and deserves further study. At this time it appears more likely that ghrelin suppression is due to interference with neural inputs to ghrelin cells rather than nutrient regulation.

Increased secretion of $PYY_{3–36}$ and GLP-1 from ileal L-cells caused by dumping of nutrients after RYGB is the most plausible explanation for the beneficial effects on glucose homeostasis and suppression of food intake. Although considerable evidence suggests that these two peptides act directly on the brain, vagal afferents may also participate. Thus, the enhanced suppression of food intake after RYGB could be partly mediated by vagal afferents in the celiac and gastroduodenal abdominal branches. These branches should not be damaged by the surgery. A role for vagal efferents in the control of PYY and GLP-1 secretion has also been reported. The strongest evidence comes from experiments in pigs, where electrical vagal stimulation increased PYY secretion from the vascularly isolated ileum (Sheikh et al., 1989).The potential contributions of vagal afferents and efferents to the outcome of RYGB surgery could easily be tested in an animal model using selective abdominal vagotomies and chemical de-afferentations by means of locally applied capsaicin.

3.3. Vagal mechanisms affected by gastric pacing and vagal stimulation

Gastric pacing is the latest and least developed method considered for obesity therapy (Abell et al., 2006). It consists of electrically stimulating the stomach wall through a pair of serosal electrodes typically near the lesser curvature about halfway between esophagus and pylorus. Although it is assumed that mainly smooth muscle is stimulated, anything else such as vagal and non-vagal nerve fascicles, interstitial cells of Cajal pacemaker cells, and enteric neurons/fibers could also be stimulated, particularly when the pulse width of the electrical stimulation is increased. It is therefore not surprising that the effects are notoriously unreliable and irreproducible and that the mechanisms leading to anorexia and weight loss found in some reports are completely unknown. This approach is in desperate need of animal models that systematically investigate the underlying mechanisms, including a potential role for vagal afferents.

Vagal afferent stimulation is increasingly used to treat epilepsy, depression, and pain in humans (Groves and Brown, 2005). Electrodes placed near the intact cervical vagus are stimulated to preferentially activate thin myelinated vagal afferents. In a preliminary study in 21 patients without a non-stimulated control group, vagal nerve stimulation did not decrease body weight over an average of 20 months (Koren and Holmes, 2006).

3.4. Role of vagal innervation of pancreas, liver, and other abdominal organs

The vagal efferent innervation of the pancreas was extensively investigated in the late 70s and 80s following the observation that subdiaphragmatic vagotomy prevented or reversed development of VMH-induced obesity (Inoue and Bray, 1977; Cox and Powley, 1981; Sclafani et al., 1981). Because plasma insulin levels rose in a vagal-dependent fashion immediately after placing electrolytic VMH lesions, vagally mediated hyperinsulinemia was considered one of the primary mechanisms leading to hyperphagia and fat accumulation (Berthoud and Jeanrenaud, 1979). The vagal preganglionic neurons projecting to interlobular pancreatic ganglia were identified by tracing (Berthoud and Powley, 1991), and functional studies in the rat demonstrated that they reach the pancreas mainly via the gastric and hepatic-gastroduodenal vagal branches (Berthoud et al., 1981; Berthoud et al., 1990; Berthoud and Powley, 1990; Wang et al., 1999). Because cephalic-vagal release of insulin is important for normal glucose tolerance (Siegel et al., 1980; Trimble et al., 1981), damage to the gastric vagal branches innervating the pancreas could be expected to have a negative role on glucose homeostasis. Since improvement of glucose homeostasis is one of the hallmarks of RYGB surgery, there

must be rapid compensation through vagal input to the pancreas via the gastroduodenal branch or the increased incretin release.

Although the pancreas is innervated by sparse vagal afferent fibers (Neuhuber, 1989), it appears to use the hormonal route to signal metabolic information to the brain. The pancreatic hormones insulin, amylin, and glucagon, each encodes some aspect of nutrient status and signals directly or via the liver to specific brain areas. Only glucagon's suppressive effect on food intake is mediated by vagal afferents, apparently picking up increased glucose production produced by glucagons in the liver (Woods et al., 2006).

In the liver it is mainly the vagal afferents implicated in nutrient sensing that could play a potential role in the development of obesity. Sensors for glucose levels and total available energy derived from fat and glucose oxidation with vagal afferent signaling to the brain and effects on short-term food intake have been described (Friedman, 1997; Horn et al., 2001; Langhans, 2003). Vagal afferent terminals potentially serving these functions have been traced to mainly the portal vein and the periportal space in the liver (Berthoud et al., 1992). Thus, ablation of vagal sensory fibers to the liver could be expected to increase food intake and predispose to obesity. Signals from the liver may also lead to metabolic changes independent of food intake. In a mouse model with hepatic steatosis induced by adenoviral expression of peroxisome-proliferator-activated receptor (PPAR)-γ2 in hepatocytes, metabolic rate increased, resulting in improved insulin sensitivity and loss of body weight (Uno et al., 2006). Capsaicin-induced lesion of vagal afferents in the common hepatic branch prevented these effects, suggesting that vagal afferent information from the liver may protect against metabolic consequences induced by excessive energy storage in the liver (Uno et al., 2006). Since vagal efferents in the common hepatic branch are important for the suppression of hepatic glucose production when the hypothalamic nutrient sensor is stimulated by nutrient repletion signals such as insulin or fatty acid oxidation (Pocai et al., 2005b; Pocai et al., 2005a), ablation of vagal efferents innervating the liver could play an additional supportive role in the development of obesity. In support of this, rats with selective common hepatic branch vagotomies where slightly hyperphagic and gained weight more rapidly when fed sweet milk (Kraly et al., 1986).

Vagal innervation of adipose tissue is controversial. One group reported vagal efferent innervation of abdominal and subcutaneous white adipose tissue from the dorsal motor nucleus based on viral transneuronal and conventional retrograde tracing (Kreier et al., 2002; Kreier et al., 2006). In a carefully controlled subsequent study no evidence of such vagal efferent innervation was found (Giordano et al., 2006). As earlier anterograde studies also did not find evidence for innervation of fat tissue by vagal preganglionic fibers, it is highly likely that the positive findings of Kreier et al were due to tracer leakage (Berthoud et al., 2006; Fox and Powley, 1989).

4. Conclusions

Vagal pathways innervating the gastrointestinal tract, pancreas, and liver are intimately involved in the control of assimilation, storage, mobilization, conversion, and oxidation of macronutrients. Although much is already known about vagal afferent nutrient sensors informing the brain about the short term availability of energy, many details regarding the specific transduction mechanisms in the periphery and the inter-and intra-neuronal signaling cascades disseminating the sensory information across the neuraxis are still missing. Vagal sensory information plays a crucial role in the mechanism of satiation but the underlying circuitry in the caudal brainstem and higher up in the brain is still ill defined. Given this central role between the brain and nutrient-handling periphery, it could be expected that the integrity of the vagal system is directly linked to the development of obesity, but this has not yet been

demonstrated. Vagal lesions have surprisingly small effects on energy balance. However this could be misleading, as typically used vagal lesions are not selective enough and the adequate challenges may not have been uncovered. The recent success with bariatric surgeries to reverse obesity highlights the importance of gut-brain and brain-gut communication. The development of animal models will clarify the role of vagal mechanisms in this presently most efficacious obesity treatment.

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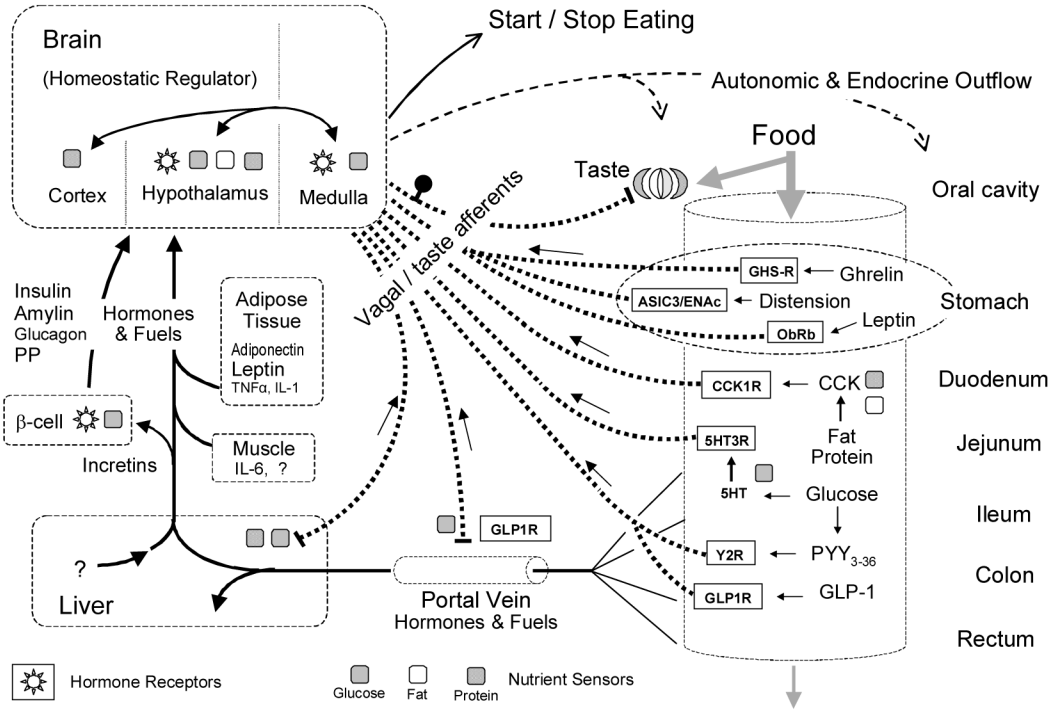

Fig. 1. Nutrient sensing in the alimentary canal and the control of food intake

Simplified schematic diagram showing the major pre- and postabsorptive transduction sites and mechanisms for the detection of ingested food and its macronutrient components. Nutrient information is sent to the brain through vagal and taste afferents (heavy dotted lines) or through the blood circulation (full lines). Specific receptors expressed by vagal afferent neurons are shown in rectangular boxes. Specific sensor mechanisms demonstrated for glucose, amino acids/proteins, and lipids/fatty acids are shown by gray, striped, and white squares, respectively.

Fig. 2. Vagal afferent mechano- and nutrient-sensors in the rat gastrointestinal tract

Vagal afferent fibers and terminal structures were anterogradely traced with the fluorescent dye DiI (bright white) injected into nodose ganglia. **A:** Intramuscular array (IMA) in longitudinal muscle layer of gastric fundus. Arrow indicated parent axon entering the muscle layer from myenteric plexus. The inset shows vagal afferent fibers in intimate anatomical contact with Interstitial Cell of Cajal. **B:** Intraganglionic laminar endings (IGLE) in myenteric plexus of gastric fundus. Two different parent axons are indicated by arrows. Myenteric ganglion is indicated by arrowheads. **C:** Mucosal endings close to epithelium (e) in villous of proximal duodenum.

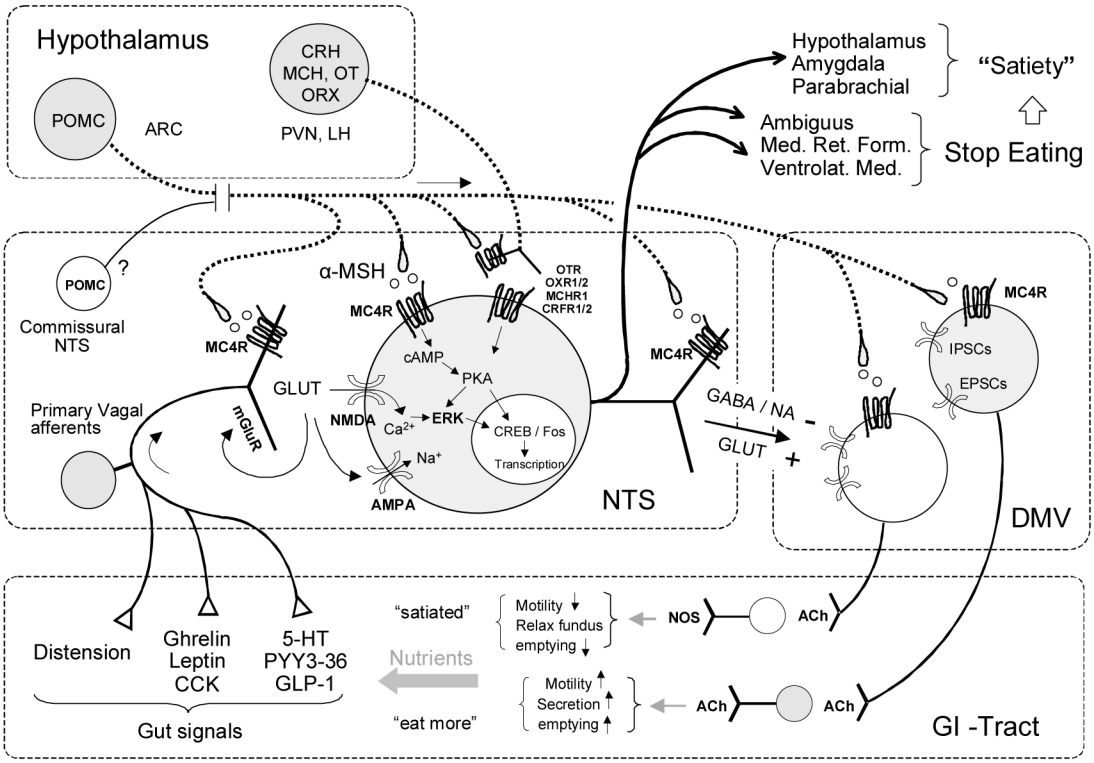

Fig. 3. Simplified schematic diagram showing the neural systems responsible for satiation and meal size control

Hypothetical neuron in the nucleus tractus solitarius (NTS) receives information from gastrointestinal mechano- and chemo-sensors through vagal afferents and projects back to the gut via vago-vagal reflexes through the dorsal motor nucleus (DMV). Other outputs (heavy lines) of certain NTS neurons are directed towards the medullary reticular formation (Med. Ret. Form.) and eventually to brainstem motor nuclei responsible for oromotor control necessary to start and stop eating, as well as to forebrain areas, responsible for sustained satiety. Descending modulatory projections from hypothalamic areas are also shown (heavy dotted lines).

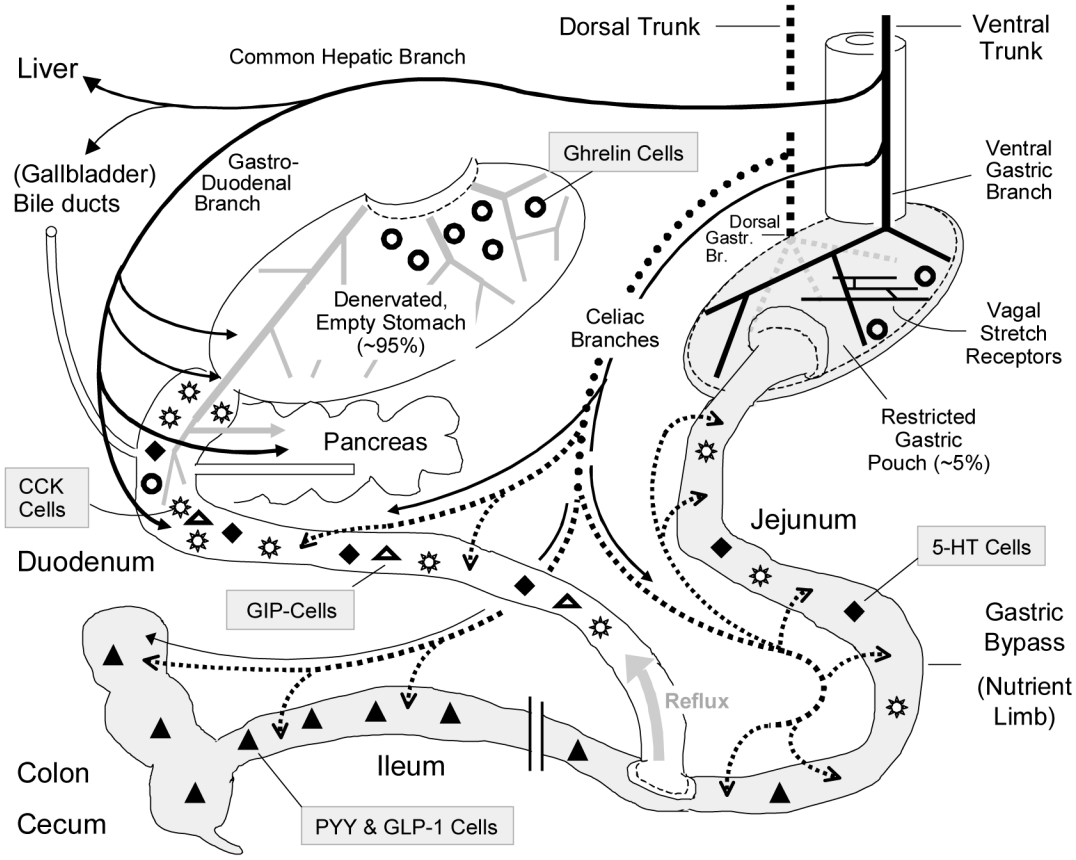

Fig. 4. Schematic diagram showing implications regarding vagal innervation and endocrine functions of gastric bypass surgery

The nutrient limb of the Rou-xen-Y gastric bypass consisting of the small gastric pouch and the anastomosed jejunum is shown on the right (shaded). The bilio-pancreatic limb including the large gastric remnant with attached duodenum and proximal jejunum is shown on the left. Note that the stomach remnant is depicted at a much reduced size for clarity. The ventral (anterior) and dorsal (posterior) vagal trunks and their branches are shown as solid and dotted lines, respectively (the severed ventral gastric branches are in light gray). The relative density and distribution of enteroendocrine cells secreting peptide hormones or transmitters are depicted by different symbols as indicated.