

Vagal Nerve Function in Obesity: Therapeutic Implications

John G. Kral · Wencesley Paez · Bruce M. Wolfe

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Abstract The primal need for nutrients is satisfied by mechanisms for sensing internal stores and detecting food; ATP is the most primitive signal. With increasing density of sensory neurons and glia (the primordial brain) and the emergence of autonomic neural activity throughout the endoderm, transmitters and other signaling molecules enable alimentation before the appearance of innate storage functions. Memory and, ultimately, cognition are prerequisites for processing and producing food to facilitate assimilation and safeguard the supply of nutrients. The gut–brain–gut axis via the vagus nerve is the autonomic neurohumoral pathway integrating these elements of energy homeostasis. Humans uniquely override obligate nutrient needs, eating in the absence of deprivation, resulting in pathological chronic overnutrition arising from dysautonomia. Obesity surgery circumvents powerful redundant mechanisms of alimentation and reduces excess stores of body fat from chronic overnutrition while preventing re-accumulation of fat. All bariatric operations, whether purely restrictive, maldigestive and malabsorptive, or combinations, rely on regulatory mechanisms related to autonomic nervous system function and the brain–gut axis. We review the functional anatomy and the importance of the vagus nerve for maintaining maladaptive chronic overnutrition and describe interventions to abrogate its

effects. In aggregate, the preponderance of evidence supported by laboratory and clinical mechanistic studies interrupting abdominal bi-directional vagal transmission demonstrates that the majority of patients report less “hunger” and lose weight.

The pathogenesis of chronic overnutrition

Life requires securing a “eunutritive” state of homeostasis in which anabolism (conversion of assimilated food into protoplasm) and catabolism (degradation of protoplasm into waste products) and energy to support function are in equilibrium. Throughout evolution undernutrition has prevailed, resulting in selection of organisms coping with periodic undernutrition in the absence of serious infection, predation, or catastrophe. Physiological processes serving anabolism have had greater survival value than catabolic processes, and, indeed, there is a preponderance of powerful, redundant, “rewarding” neuronal pathways that mediate anabolism. Substrate depletion triggers autonomic counter-regulatory mechanisms.

“Stress” is the result of any condition that threatens structural or functional integrity, disrupting homeostasis. Disequilibrium causes stress resulting in dysautonomia. Human evolution more than that of other species, exhibits qualitative and quantitative increases in the ability to respond to stressors, ultimately giving rise to cognitive processes to counteract stress and preserve energy (e.g., hunting, cooking, farming, refrigerating).

Hyperacute stress releases catecholamines, which initially blunt appetite while mobilizing glucose from hepatic glycogen. This contributes to a condition of acute undernutrition, which stimulates other “stress hormones” (e.g., corticotropin releasing factor, cortisol), with reciprocal

J. G. Kral (✉)
Department of Surgery, State University of New York
Downstate Medical Center, 450 Clarkson Avenue, Box 40,
Brooklyn, NY 11203, USA
e-mail: jkral@downstate.edu

W. Paez · B. M. Wolfe
Department of Surgery, Oregon Health and Science University,
3181 S.W. Sam Jackson Park Rd., Portland, OR 97239-3098,
USA

effects on ingestive behavior ultimately attenuated by ingested nutrients [1]. Interestingly, cortisol increases small intestinal substrate uptake [2]. Stress leads to fast eating (or “gorging”) in several species, which led Kral to postulate that fast eating is an early mediator of a hyper-anabolic state of chronic overnutrition underlying dysregulation of autonomic nervous system function, immune response, growth, regeneration, and reproduction [3, 4].

Ingestive behavior

Fast eating is rewarding, stress-reducing, and resuscitating, but it has several adverse consequences. Repeated (over-)distension of the esophagus and fore-stomach (phasic, as in large bolus ingestion; tonic, as in increased intragastric pressure) causes “acquired Hirschsprung’s disease of the foregut,” with reductions in neurons, pacemaker cells (Cajal), and potentially, enteroendocrine cells [4]. Furthermore, rapid eating causes higher peaks of insulin and incretins, ultimately causing downregulation of insulin receptors and β -cell exhaustion. In addition, it leads to accommodation of gastropancreatic reflexes and overstimulation of enterocytes (absorptive) and enteroendocrine cells with post-ingestive glycemia [5] and lipemia [6], components of the insulin-resistant metabolic syndrome.

Substrate-product disequilibrium can either result in excess deposition of nutrients or in depletion of essential nutrients. By increased rate of delivery and concentration of substrates and hormones to target tissues according to a topographic-hierarchical order (e.g., gut wall, lymph, liver, adipose tissue, and “ectopic” sites), rapid eating with increased rate of gastric emptying ultimately leads to nutritotoxicity (gluco-, lipo-, nitro-toxicity, uremia, azotemia, uric acid excess) manifested as T2DM, atherosclerosis, metabolic obesity, gout, vascular reactivity changes, immune compromise, or carcinogenesis, as first proposed in the “metabolic sink” hypothesis [7]. During equilibrium sympathoadrenal activity mediates dietary thermogenesis and gastrointestinal hypermotility, the only two mechanisms for handling temporary substrate overload.

Abdominal vagal efferent activity initiated during the anticipatory cephalic phase modulates gastrointestinal secretomotor release of digestive gastric and pancreatic juices and anabolic hormones such as insulin and cholecystokinin (CCK), followed by afferent activity and direct effects of nutrients. Anticholinergic drugs and vagotomy both reduce gastric and pancreatic secretion and delay gastric emptying of solid food. Thus complete abdominal vagotomy reduces anabolism and counteracts fast eating and its sequelae [8, 9].

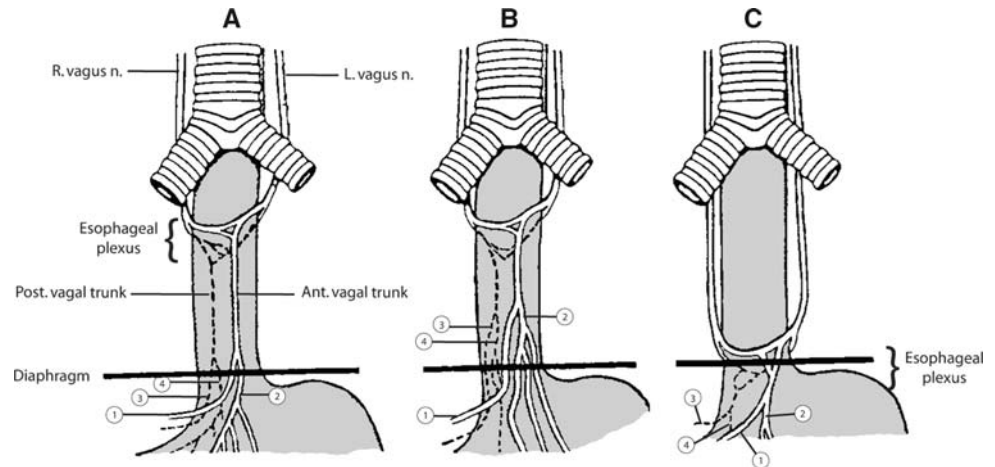
Abdominal vagus nerve and vagotomy

Peptic ulcer disease

Although described in the nineteenth century [10, 11] and developed by Latarjet in the 1920s [12], vagotomy was not given a leading role in ulcer treatment until Lester R. Dragstedt published his first clinical paper in 1943 [13]. The major conclusions of 60 years of intensive laboratory and clinical investigation of subdiaphragmatic vagotomy for ulcer disease, relevant for assessing the current status of the procedure can be summarized as follows:

1. The numbers and locations of trunks and functional vagal fibers in the human abdomen are variable, in aggregate always exceeding two [14, 15]. There are important differences between the anatomy of the branches of the abdominal vagus in rodents, cats, and humans, rendering complete vagotomy more difficult in people. It is true that there are two main vagal trunks at the level of the hiatus and the cardia, but resecting these two trunks alone guarantees an incomplete vagotomy owing to numerous functionally important vagus nerve branches in this region (Fig. 1). The anatomy in question has been studied and described in great detail in several publications during the heyday of vagotomy for ulcer disease [15] and toward the end of the era of elective peptic ulcer surgery [14]. This knowledge is relevant for two reasons: (1) it informs those who wish to achieve complete vagotomy and (2) it provides perspective to the claims that inadvertent or incidental vagotomy might explain mechanisms of standard bariatric operations.
2. Achieving complete vagotomy, a major issue in the field, requires careful skeletonizing (baring or “denuding”) of the distal 5 cm of the esophagus, including resection of extra-esophageal pre-aortic and “hepatic” branches [16, 17] and performing intraoperative and postoperative tests of completeness [18, 19] in addition to sending specimens for histopathology. It is important to resect several centimeters of nerve fibers, indeed, a *vagotomy*, which might explain differing recurrence rates compared to simple transection (see 5. below).
3. There are several methods for assessing vagal integrity, three of which are used intraoperatively: (1) Leukomethylene blue stains nerve tissue light blue, appearing much lighter than the surrounding esophageal tissue. (2) Electrostimulation at the level of the cardia elicits gross motor contraction in the presence of intact vagal innervation. (3) Intraoperative gastroscopy, spraying the fundic mucosa with Congo-red dye after systemic administration of a cholinergic drug,

Fig. 1 Where four or more vagal structures emerge through the hiatus, they may be **a** divisions that have separated just above the diaphragm; **b** divisions and their branches that arise above the diaphragm; or **c** elements of the esophageal plexus that extend below the diaphragm. The vagal trunks are entirely within the abdomen. 1 = hepatic division; 2 = anterior gastric division; 3 = celiac division; 4 = posterior gastric division. (From [14].)



identifies areas with intact innervation, which turn black [18]. Numerous drugs are used to stimulate efferent vagus activity, including insulin, histamine or betazole, pentagastrin, and Baclofen, a GABA B receptor agonist [20–22], although anesthesia may be a confounding factor intraoperatively. Physiological tests of vagal integrity include modified sham feeding (“chew-and-spit”) in conjunction with measuring acid output and/or plasma levels of pancreatic polypeptide (PP), urine pH (“acid tide” [23]), and a novel thirst test using an osmolar challenge [24, 25].

4. Although <20% of vagus fibers are efferent (secretomotor) and have been studied vastly more than the more numerous afferent (sensory) fibers, there are complex interactions between the afferent and efferent pathways, ranging from the spinal to the central nervous system level and acting during different phases of the alimentary process important for regulating energy balance.
5. Reciprocity of parasympathetic and sympathoadrenal tone leads to increases in sympathetic tone pursuant to complete vagotomy, significantly affecting energy balance. The vagus nerve contains both parasympathetic and sympathetic adrenergic fibers that can either be stimulatory or inhibitory and that use different molecules for transmission, complicating scientific analysis of pathways but likely of no clinical importance.
6. After “complete” abdominal truncal vagotomy, there is compensatory “sprouting” or recruitment of patent vagal nerve fibers and likely regeneration of vagal innervation, leading to re-emergence of some vagal functions. The time frame for vagus nerve regrowth or recruitment in humans is not known, nor is it known whether regrowth affects specific functions differentially. Three rodent studies indicate that there is relatively rapid re-innervation by afferent fibers, but

not by efferent fibers, after abdominal vagal transection [e.g., 26].

7. The quantitative or “dose–response” relationships between degree of completeness and loss of vagal functions, whether afferent or efferent, are not known in humans, although there are recent data from rodents [27]. It has never been determined precisely which, if any, functions of the vagus nerve, whether efferent or afferent, might be retained after routine abdominal surgical vagotomy for ulcer disease.
8. Drainage operations (pyloroplasty, gastroenterostomy), earlier considered mandatory for open transthoracic or transabdominal operations for peptic ulcer disease, have been proven to be unnecessary with or without transgastric dilation of the pylorus [28, 29]. There is no evidence of the need for any drainage intervention in *non-ulcer* patients undergoing vagotomy. When Dragstedt introduced vagotomy for the treatment of duodenal ulcers in 1943 (after a decade of studies proving the importance of gastric acid in ulcerogenesis), he performed transthoracic vagotomy [13]. Among his first 39 operations for ulcers, 3 patients required subsequent gastroenterostomy, prompting him to start performing this routinely at the time of vagotomy in patients with evidence of pyloric stenosis. Although he started to use a transabdominal approach, the vagotomies were still supradiaphragmatic, opening the hiatus. Among 350 vagotomies published in 1948, 144 (56 transthoracic and 88 transabdominal) did not include drainage procedures [30].
9. Effects, side effects, and complications of complete abdominal vagotomy are benign, the latter being mild and relatively rare. When evaluating effects, side effects, and complications of vagotomy without drainage, it is critical to take several points into consideration: (1) the approach (laparoscopic versus open;

transthoracic versus abdominal), (2) the level (supradiaphragmatic: how high above the cardia?), (3) the completeness, and (4) the precise indication for the operation, recognizing the patient's and the surgeon's expectations of outcome.

Effects and side effects of vagotomy

Vagotomy impairs gastric adaptive relaxation (GAR) initiated by the cephalic phase of food ingestion and maintained as food more than liquid traveling distally distends the esophagus. Related to reduced GAR, vagotomy increases the tone of gastric muscle and pylorus, thus decreasing the capacity for storage of solids, delaying their emptying while increasing the emptying rate of liquids through the open, yet somewhat constricted pylorus [31]. Increased gastric wall tone may increase intragastric pressure, slowing esophageal transit, which exceedingly rarely may be experienced as *dysphagia*.

These effects result in *gastric stasis* of solids, decreasing intake, and in rapid transit of liquids. Volitional intake of solids exceeding the reservoir capacity of the stomach may lead to *vomiting* and to gastric distension, which in extreme cases may cause *atony* of the stomach. These side effects have been reported mainly after supradiaphragmatic vagotomy for ulcer disease and not after abdominal vagotomy for obesity. They are rare because gastric sympathetic and non-adrenergic, non-cholinergic (NANC) pain pathways signal the patient to stop eating; vagotomy has been demonstrated to enhance sensitivity to substance P, a key mediator of pain, interestingly implicated in mechanisms of tissue repair [32]. Furthermore, truncal vagotomy abolishes gastric hunger signals and those related to hypoglycemia [33–35], a result that is most highly desired by obese patients.

Gastric stasis, especially of solid food rich in bacteria, may be associated with bacterial overgrowth in the hypochlorhydric milieu, contributing to foul-smelling *burping*, and *diarrhea*. This is treatable by consumption of acid liquids and, as needed, by a course of antibiotics.

Rapid emptying of liquids may also contribute to *diarrhea* and to *dumping*, mostly attributable to drainage procedures [36]. These side effects, although supportive of weight loss (through aversive conditioning), can be managed through patient education and even with medication. They are rare in patients without drainage procedures and are invariably transient in nature, disappearing within 12–18 months. Furthermore, vagotomy in itself leads to a spontaneous decrease in the consumption of liquids [37].

Long-term side effects of vagotomy performed for ulcer disease include various mild and asymptomatic *deficiencies*

of vitamins and minerals, easily preventable by monitoring and over-the-counter supplementation.

Complications of vagotomy

The standard complications of laparoscopic operations are also the complications of vagotomy. The most serious are perforations of the viscera, in particular the esophagus. Risks of bleeding and infection are exceedingly rare in the hands of experienced laparoscopic surgeons, who have the benefit of magnifying laparoscopes and the means of testing for leaks during the course of the operation.

Obesity

Background

The role of the vagus nerve in appetite regulation was recognized in the late nineteenth century [38]. A fascinating study of the vagus nerve in 11 crocodiles and 2 alligators published in 1886, described significant weight loss with shrinkage of the fat body after bilateral cervical vagotomy [39].

The lipostatic hypothesis of energy regulation [40, 41] provided evidence for hypothalamic origins of adiposity in agreement with the pioneering lesion experiments of Hetherington [42], Brooks [43], and Brobeck [44]. Clinical correlates were well recognized in rare cases of tumors [45] and their treatments [46, 47]. Powley [48] demonstrated, as had others [49], that abdominal vagotomy prevented or mitigated hypothalamic obesity in rats, later shown to be independent of gastric dysmotility [50]. Furthermore, long-term clinical studies of vagotomy performed for ulcer disease demonstrated weight loss, mainly attributed to maldigestion and malabsorption of fat [51–53].

Motor fibers, comprising <20% of the vagus, govern gastric acid and pepsin secretion, motility, adaptive relaxation, and secretion of foregut peptides, most notably insulin and incretins, initiated during the *cephalic phase* of digestion. Cephalic phase responses, which initially are afferent, affect meal size as well as motivation to feed, and they are abolished by abdominal vagotomy. Afferent vagal fibers, while intimately linked to efferent functions, transmit diverse signals pertaining to “hunger” and “satiety” (orexigenic and anorexigenic). Chemo- and osmosensors relay homeostatic signals of tissue hydration and energy stores, whereas mechanoreceptors sense gastric fullness. Recently identified and synthesized appetitive neuropeptides and molecules are mediators of nutrient sensing and activate peripheral, predominantly vagal, and central nervous system receptors. Examples of such peptides are ghrelin, cholecystokinin (CCK), peptide YY (PYY),

orexin, glucagon-like peptide-1 (GLP-1), and neuropeptide Y (NPY), pro-opio-melanocortin (POMC), and agouti-related peptide (AgRP) (Fig. 2).

Both afferent and efferent vagal mechanisms are thus involved in both “hunger” and “satiety.” Theoretically, by disrupting transmission of satiety signals, vagotomy might be expected to cause increased food intake, weight gain and obesity. Extinguishing or attenuating “hunger” or appetite, obligate physiological precursors of ingestion, on the other hand would pre-empt post-ingestive satiety signals. Indeed, complete transection of abdominal vagus nerve fibers has consistently abrogated weight gain or caused weight loss in all studied species (mouse, rat, crocodile, rabbit, dog, monkey), including humans. Although there are several candidate mechanisms, animal studies have not determined the relative importance of any individual mechanism or combination of mechanisms to explain the effects of truncal vagotomy on energy balance.

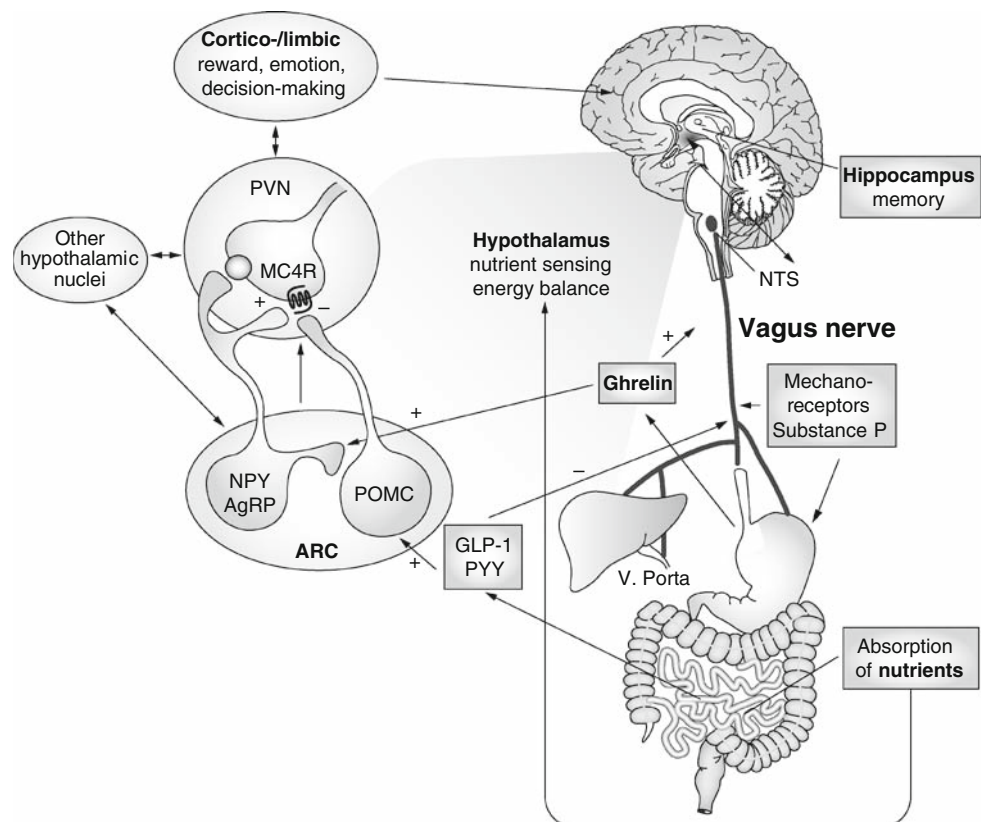
Clinical studies

Kral, during his studies of lipostatic mechanisms [57, 58] and the gastrointestinal physiology of severely obese intestinal bypass patients [59], performed a pilot study in Sweden of subdiaphragmatic truncal vagectomy as a

stand-alone operation for severe obesity [60]. These studies were based on the hypothesis that “common obesity” has hypothalamic origins. The patients in Kral’s studies exhibited significant weight loss, a finding that was replicated in a small series of transthoracic vagotomies performed by J. S. Kirkham in London [61]. In the latter series, there was a higher initial prevalence of transient complications, likely owing to the increased ease of achieving complete vagotomy via this approach.

Vagotomy as treatment for obesity received little further attention, likely because of the greater efficacy of gastrointestinal bypass and purely gastric restrictive procedures (“gastroplasty”) over the short term in severely obese patients with BMI > 40. Vertical banded gastroplasty (VBG, the predominant procedure of the 1980s and 1990s), performed as a rescue operation in vagotomy patients dissatisfied with the short-term rapidity of weight loss, exhibited potentiated long-term weight loss comparable to results after gastric bypass. For this reason Kral and Görtz used vagotomy as a rescue operation after gastroplasty, and they presented a small randomized study comparing gastroplasty plus vagectomy to vagectomy alone [62]. A Polish study from 1993 describes “subjects treated by truncal vagotomy and gastric banding a few years earlier” without providing any comparative results [63].

Fig. 2 The brain–gut axis: appetite regulation via bidirectional vagal signaling. Cortical influences represent higher brain centers which, together with the limbic system, can override autonomic function in humans. Vagotomy reduces ghrelin, which normally stimulates appetite during substrate depletion and has direct orexigenic effects on neuropeptide Y (NPY) neurons in the arcuate nucleus (ARC), the receptive brain region for vagal appetitive signaling [54–56]. (The illustration does not include sight, smell, and taste or adipose tissue input.) *AgRP* Agouti-related peptide; *GLP-1* glucagon-like peptide 1; *MC4R* melanocortin 4 receptor; *NTS* nucleus of the solitary tract; *POMC* pro-opiomelanocortin; *PVN* paraventricular nucleus; *PYY* peptide YY



Introduction of laparoscopic approaches into routine surgical practice has substantially improved the safety of operating on severely obese patients, who are at increased risk of operative complications of any laparotomy. Laparoscopic truncal vagotomy has been perfected and proven safe and effective for ulcer disease [64]. For obesity, truncal vagotomy is a less invasive procedure than gastrointestinal bypass operations requiring anastomoses. It is also associated with fewer and milder side effects than gastric banding, an approach that requires considerable behavior modification to achieve durable weight loss.

With the substantial need for effective treatment of obesity at younger ages and the improved safety of laparoscopic procedures, it is now recognized that surgical treatment is justified at lower levels of BMI, before the eating disorder has become intractable requiring malabsorptive operations [65]. A dual-center “open-label” study of stand-alone laparoscopic abdominal vagotomy was undertaken starting in 2006 [66]. At 18 months 15 of 19 evaluable patients exhibited mean percent excess weight loss (%EWL) of 17.6 (range: +8.5 to –69% EWL), with mild and transient side effects. Two prospective trials comparing laparoscopic adjustable banding with and without truncal vagotomy have been in progress since 2006 [67, 68]. In the series from North Carolina, 10 patients with vagotomy plus adjustable banding had 53.6% EWL at 1 year compared to 40.7% in 12 control patients with banding alone ($p = 0.03$). At two years there are too few patients for meaningful evaluation, although the trend persists (65% in 6 patients with vagotomy versus 44% in 9 patients with banding alone; $p = 0.06$).

In aggregate, over the short term these small studies have replicated Kral’s findings in similar severely obese patients undergoing open vagotomy: side effects and complications are transient and milder, whereas weight loss is slower than with other surgical treatment but more rapid and greater than described after nonoperative methods. In the head-on comparisons adding truncal vagotomy to adjustable banding, weight loss is potentiated with no differences in complications or side effects, time to band inflation is prolonged [67], and numbers of adjustments are fewer, with patients reporting less “hunger”.

Long-term follow-up

After a mean 20 years (range: 12–30 years) follow-up of 90% of Kral’s patients in Sweden with vagotomy alone or in conjunction with gastroplasty or with gastroplasty alone demonstrates 44% excess weight loss (mean BMI reduction of 8 ± 7 units [SD]) in patients with vagotomies compared to 33% excess weight loss (mean BMI loss 6 ± 5) in patients with gastroplasty alone ($p < 0.05$). All-cause mortality among the total of 99 patients, 48 with

vagotomies and 51 without, was similar (20.8 vs. 21.6%; NS) and there were no differences in side effects or complications [69]. The surviving patients are currently (May 2009) undergoing extensive study, including endoscopy, tests of completeness, glucose tolerance, and a battery of tests to evaluate adipokines and gastrointestinal hormones. The superior maintenance of weight loss in patients with vagotomy accords with the long-term weight loss described in ulcer patients [52, 53].

Intentional abdominal vagotomy performed during bypass operations

Indications for performing vagotomies in gastric bypass patients have either been to prevent or to treat stomal ulcers or reflux esophagitis, which means that neither prospective nor retrospective controlled analyses of weight or comorbidity reduction have been performed. Mason described “usually” adding vagotomy when reducing pouch size in gastric bypass patients with stomal ulcers [e.g., 70], whereas Torres routinely did it during Roux-en-Y gastric bypass in 71 patients to prevent stomal ulcers [71], and Buckwalter described using vagotomy for reflux esophagitis in 6 patients [72]. Alden in Minnesota and Catlin in California did vagotomies at the time of gastric bypass in obese ulcer patients. Upon request, they performed retrospective chart reviews of the weight loss and complication rates of vagotomized patients compared to contemporaneous obese non-ulcer patients; they did not observe any significant differences according to personal communications.

In 1986 in an early series of 33 patients who underwent biliopancreatic bypass, Biron et al. replaced the Scopinaro partial gastrectomy in 17 patients by performing *selective* vagotomy with closure of the duodenum in continuity, achieving equivalent short-term results [73]. Over the long term, however, the duodenal closure opened, persuading the surgeons to abandon this procedure. An editorial in 2004 based on a case report with gastric dilatation as a complication of gastric bypass while performing reversal of intestinal bypass assumed this complication to be caused by vagotomy, prompting the authors to caution against vagotomy without drainage in this context [74].

Taken together, although lacking descriptions of technique and in the absence of tests of completeness of vagotomies, there are no data to support performing vagotomy for the purpose of potentiating weight loss at the time of diversionary operations. Indeed, all analyses performed to date, although reported in small uncontrolled series, have failed to demonstrate any weight loss advantage when adding vagotomy to a diversionary operation.

Hypothetical vagotomy or vagal dysfunction after gastric operations

At present there is much speculation about the role of vagotomy as a mechanism for explaining inter-study differences in levels of the most powerful peripheral orexigenic hormone, ghrelin [75, 76], and [related] weight loss after laparoscopic gastric bypass. Intentional complete vagotomy in rats does block prandial release of ghrelin [77], as it does in people [55]. It is true that separation of the gastric pouch from the corpus during laparoscopic gastric bypass might diminish net ghrelin production or secretion, just as excision of the fundus during sleeve gastrectomy as a stand-alone procedure causes denervation and/or excision of fundic parietal cell mass. It is not likely, or even possible, however, that either denervation (vagotomy, not vagectomy) or resection is complete in this context. Thus, in the absence of protracted serial studies of ghrelin production and secretion, it is impossible to know the magnitude of any putative reduction in the appetitive effects of circulating ghrelin. At the same time it is certain that any incidental vagotomy performed in conjunction with gastric bypass would fail to transect all afferent vagal signaling related to ghrelin receptor activity in the nerve.

There is similar speculation that an inflatable circum-gastric band, even uninflated, has appetitive effects attributable to vagus nerve function. One study of weight-stable patients 26 months after adjustable gastric banding demonstrated that they experienced less “hunger” after an overnight fast with undefined “optimally” inflated bands than with uninflated bands, the latter satiety ratings being equivalent to those of weight-matched unoperated controls [78]. The effects were attributed to altered “neural and hormonal messages arising from the area.” Inflation versus deflation exerted no effects on serial measurements of ghrelin or on insulin. Thus it is unlikely that messages are mediated by vagal satiety signaling, as demonstrated in patients with vagotomy combined with adjustable banding.

Alternative vagus-related interventions

Electric

Studies of stimulation of the stomach wall by means of “gastric pacing” with an implantable gastric stimulator (IGS) are in progress [79]. It has not been determined to what extent electrostimulation of the muscularis of the stomach affects vagus nerve function, although levels of vagally regulated gastrointestinal hormones were reduced after 6 months of chronic stimulation, whereas ghrelin levels increased and paradoxically correlated with the magnitude of weight loss [80]. A mechanistic

neuroimaging study employing IGS demonstrated effects in key areas known to mediate reward and impulse control [81], implying mediation through vagal pathways.

Clinical studies of IGS have focused on developing “screening algorithms” to detect potential responders, employing numerous exclusion criteria. Nevertheless, a recent randomized, placebo-controlled, double-blind, multi-center study of 190 severely obese patients followed for 12 months did “not support [IGS] application” [82]. Laboratory work is still in progress to identify novel stimulation strategies related to timing and placement of electrodes in the hope of finding a clinically useful alternative to vagotomy. A pilot study of a stimulator activated by gastric motility during ingestion, causing increased rate of gastric emptying, exhibited mixed results after 1 year [83]. The investigators attribute the mechanism of weight loss to “gastric contractility modulation,” which they subsequently have applied to patients with type 2 diabetes mellitus, with promising short-term results [84].

Vagus nerve electrostimulation (VNS) using a pacemaker applied to the cervical vagus nerve is used routinely for intractable epilepsy after more than a decade’s experience, and it has been employed more recently as adjunctive therapy for depression. There are conflicting reports concerning weight loss during VNS for epilepsy [85, 86], although a recent study demonstrated robust weight loss in depressed obese patients treated for 2 years [87]. It has been proposed that retrograde vagal stimulation via the nucleus of the solitary tract (NTS) in the brain stem to the amygdala and other hypothalamic centers affecting reward and energy metabolism is responsible for the weight loss [88].

Electrical impulses delivered to the subdiaphragmatic vagal trunks have been used to “intermittently block both vagi” in animal experiments and in recent short-term clinical studies. The investigators in an open-label study placed an implantable device ($n = 31$) using high-frequency electrical impulses to intermittently block two vagus nerve trunks. Patients saw excess weight loss of 7.5% at 4 weeks, 11.6% at 12 weeks, and 14.2% at 6 months ($p < .001$). Moreover, patients were noted to have decreased inter-meal “hunger” and earlier intra-meal satiation [89]. The impulse frequencies were based on previous animal studies, which showed vagal inhibition of pancreatic polypeptide exocrine secretion [90, 91]. Although most investigation has been directed toward vagal efferent function, which is clearly blocked, patients often give identical reports of absence of “hunger” similar to patients after vagectomy, implying abolition of the (afferent) cephalic phase of alimentation. Interestingly, electro-acupuncture (transcutaneous electrical nerve stimulation; TENS), directly affects peptides in the arcuate

nucleus (Fig. 2) and has been demonstrated to cause significant short-term weight loss in obese subjects [92].

Endoscopic

Techniques developed so far employing natural orifice transluminal endoscopic surgery (NOTES) have not yet generated procedures known to affect vagal function, although vagotomy via a 7 mm transesophageal incision was recently described in a pilot study in pigs [93]. A newly developed transesophageal endoscopic device employing high-frequency ultrasound to identify and necrose vagus nerve fibers has yet to be placed in a clinical trial.

Endoscopic intraparietal gastric injection of botulinum toxin, a potent neurotoxin that blocks acetylcholine release, is being studied clinically, demonstrating facilitation of weight loss over the short term [94]. Most of the clinical research has focused on gastric motility, although reports on satiety associated with toxin injections in the fundus imply abrogation of ghrelin-mediated vagal afferent effects. The short duration of efficacy and tolerance to botulinum toxin limit its therapeutic potential. A different method of achieving ghrelin suppression, by selective chemical embolization of gastric arteries supplying the fundus, has been described in growing pigs. During 4 weeks of observation there were statistically significant reductions in serum ghrelin and weight gain [95]. It remains to be seen whether this technique can be safely adapted in obese patients, providing more than transient effects on body weight.

Pharmacological

Although a detailed discussion of medications is beyond the scope of this review, it is notable that the anticholinergic effects of antiepileptic and antidepressant drugs include weight loss, similar to that observed from vagal electrostimulation for these same conditions. There are consistent observations of weight loss from antiepileptics and several antidepressant serotonin (5HT) reuptake inhibitors [96], although there is controversy concerning whether this is an independent effect of the drug (given the role of serotonin in sugar craving) or secondary to improvement of the depression. Nevertheless classic antimuscarinic vagolytics, such as atropine and hyoscyamine, have been thoroughly studied for weight loss but proven impractical at effective doses, owing to side effects such as dry mouth, blurring of vision, constipation, orthostatic hypotension, and cardiac arrhythmias, as well as other adverse effects.

The most studied anticholinergics have exclusively exhibited vagal efferent effects related to the conditions for

which these drugs were prescribed, with no descriptions of afferent effects. Interestingly there are recent reports of reduction of mesenteric adipose tissue (“visceral obesity”) from capsaicin, the nerve-numbing substance in red chili peppers used experimentally to inhibit afferent nerve transmission. The effects are attributed to vanilloid receptors on vagal nerve fibers [97].

Directions for future research: methods and applications

Central nervous system function

Recent progress in functional neuroimaging has enabled detection of structures specifically activated by appetitive factors, validated by verbal reports of subjective experiences of “hunger” and “satiety” and prediction of ad libitum food intake. Although these techniques are prone to methodological errors [98], they could elucidate some of the differences in functional central nervous system pathways activated before and after different bariatric operations. Such studies allow assessment of intrinsic effects of band placement, with and without inflation. Alternatively, event-related brain potentials that differentiate between states of satiety and food deprivation during electroencephalography [99] might similarly be useful for studies of different operations.

Functional magnetic resonance imaging (fMRI) was just described in anesthetized gavaged rats with and without vagotomy, demonstrating the post-oral gut–brain communication of intragastric nutrition [100]. Similar studies in humans would circumvent the serious limitations of anesthesia, gavage, which excludes the important cephalic phase, and the use of an irrelevant rodent. In addition to the report on vagal stimulation in depressed patients [87] and the positron emission tomography (PET) scan study of IGS for obesity [81], fMRI has been used during balloon distention in obese patients [101] as has PET scan and 2-deoxy-2[18F] fluoro-D-glucose [102] enabling localization of vagal afferent correlates in the brain. Electroencephalography or functional neuroimaging have yet to be applied to assessment of vagotomy in people.

Genetics, epigenetics

Although laboratory animals are of limited relevance for the study of the hedonic and cognitive factors and the neurobiology of decision making that underlie motivated behavior such as eating in humans, recent progress in gene manipulation may be applied to candidate genes known to be involved in vagal afferent innervation mediating ingestive behavior [103]. It is true that autonomic nervous

system genes and polymorphisms have been described in people [104, 105], including those specifically linked to obesity [106], but transgenic rodents allow mechanistic studies not yet possible in humans. The rapid advances in epigenetics, identifying numerous candidate genes exhibiting epigenetic (environment-susceptible) changes affecting obese and diabetic phenotypes [e.g., 107, 108] have yet to be applied to vagal or other autonomic nervous system functions.

Electrophysiology

Just as appetite suppressant (autonomic nervous system) drug treatment, only used for relatively short periods of time and long after discontinuation of treatment, exhibits neurotoxicity in people [109], it is conceivable that bidirectional chronic vagus nerve stimulation might damage brain axons or target nuclei. Absence of local pathological changes in relatively short-term studies of vagus nerve tissue in rodents is insufficient to rule out this type of problem from chronic continuous or intermittent vagus nerve stimulation. Abdominal vagotomy uniquely provides the largest and longest clinical experience of any specific intervention intentionally directed toward healthy neuronal tissue. There are no clinical data describing any long-term effects of vagotomy on rostral vagus nerve integrity or function or on changes in the central nervous system in vivo or obtained at autopsy. It is important to keep in mind that 100 years of vagotomy in clinical practice has not identified serious adverse effects. At the same time, these operations have mainly been performed in older patients.

Classic neurogastroenterology

Neurogastroenterology is a relatively new area of study, but its methods are founded in physiology, the earliest mechanistic biomedical science, which dates from the beginning of the nineteenth century. Physiology has profited immensely from new techniques such as neuron tracking using stains exemplified by horseradish peroxidase (HRP), immunochemical viral vectors, and intracellular green folding proteins to study vagal nerve function. In conjunction with microsurgical techniques of vagal afferentectomy in the brain stem [110, 111] and super-selective intra-abdominal vagotomies of rats [112], valuable information for elucidating antidiabetic and appetitive effects of antiobesity surgery, might be translated into clinical practice.

Pharmacology

In addition to the selective sensory nerve blocker capsaicin, mentioned earlier, a host of pharmacological agents

including molecules that block or activate specific metabolic pathways, such as methyl palmoxirate, 2,5-anhydro-D-mannitol, and fluoro-deoxyglucose are valuable tools validating the critical importance of visceral vagal afferent pathways to the brain. Etomoxir, a fatty acid synthesis inhibitor used in people [113] exhibits consistent appetite-stimulating effects similar to fat inhibitors shown in rodents to rely on intact vagal signaling [114]. Clinical studies of these types of pharmaceuticals using neuroimaging and visual and real food stimuli before and after various bariatric operations, with and without intentional vagotomy should contribute to the understanding and treatment of chronic overnutrition.

Conclusions: the psychoneurobiology of treating obesity

Whereas vagotomy, i.e., disruption of the gut–brain–gut axis, successfully reduces food intake and weight in all studied species living under naturalistic conditions, results in people are less robust. The reason is the unique human capacity for cognitive override of autonomic maintenance of energy balance. All surgery for obesity is “behavioral” regardless of the mechanisms of the surgery or its intent. Mechanisms can be satiating or aversive, although aversion is normally more effective than reward. The vagus nerve belongs to the parasympathetic branch of the autonomous nervous system (ANS), yet the effects of vagotomy, regardless of primary intent, have behavioral consequences, most of which can be volitionally modulated. It is for this reason that patients must be fully educated about and invested in the desired effects and side effects of any treatment they receive, even surgical. The magnitude of weight loss and co-morbidity improvement with all forms of treatment, including surgical, are directly proportional to the frequency of office visits [115, 116]. Most surgeons do not routinely perform operations in which patient cooperation is as critical as is the case in bariatric surgery, wherein lies the biggest problem with anti-obesity surgery, analogous with all treatment modalities.

Postoperative instruction regarding appetite

Patients who have had complete vagectomy as a treatment for obesity do not experience substrate depletion, deprivation, or “hunger,” defined as the gnawing, aching pains and sensations of contractions in the upper abdomen. This is desirable for someone convinced of the necessity to lose weight. Kral’s simplistic universal patient instruction to all obesity surgery patients has been: “OBEY YOUR STOMACH! Do not eat because (1) someone well-meaning (most commonly your mother) tells you to; (2) it is mealtime; (3) everybody else is eating; (4) you are afraid

that something ‘bad’ will happen to you!” Exhortations to eat have survived culturally, owing to their importance in times of famine and life-threatening infections. In the current epidemic of obesity it is critical and overdue to update nutritional messages in the interest of public health.

Kral’s patients regularly reported that they would feel weak or light-headed toward the end of the day. This likely represented “hypoglycemia awareness”—a well-studied phenomenon known to diabetologists eager for their patients to avoid iatrogenic hypoglycemia [35]. Most vagotomy patients are highly motivated to lose weight and will not force food into their stomachs, whereas ulcer patients, not fully instructed about the adverse effects of eating too much may not have such motivation. None of Kral’s [69] or Kirkham’s [61] patients developed atony, stasis ulcers, or gastric rupture after warnings about vagotomy without drainage in ulcer patients.

An overarching problem in treating obesity is the limited therapeutic “success” in the heaviest patients. Clearly there exists a “pack-year” phenomenon leading to intractability or irreversibility of co-morbidity over the long term and with increasing severity of the eating disorder, as demonstrated by the positive correlation between relative magnitude of binge-eating disorder and body mass index [4]. For this reason, we suggest that refractory obesity should be treated as early as possible in the disease process [65], enabling use of milder forms of treatment. These forms of treatment have less likelihood of succeeding in the severely obese patients, in whom indications for surgery have been based on outdated weight-based standards. We postulate that a combination of cognitive and autonomic intervention might be optimal in appropriate circumstances, as suggested above.

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