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REVIEW

The Gut and Energy Balance: Visceral Allies in the Obesity Wars

Michael K. Badman and Jeffrey S. Flier*

In addition to digesting and assimilating nutrients, the intestine and associated visceral organs play a key sensing and signaling role in the physiology of energy homeostasis. The gut, the pancreatic islets of Langerhans, elements in the portal vasculature, and even visceral adipose tissue communicate with the controllers of energy balance in the brain by means of neural and endocrine pathways. Signals reflecting energy stores, recent nutritional state, and other parameters are integrated in the central nervous system, particularly in the hypothalamus, to coordinate energy intake and expenditure. Our understanding of regulatory neural circuits and the signaling molecules that influence them has progressed rapidly, particularly after the discovery of the adipocyte hormone leptin. These discoveries have led to exploration of novel routes for obesity control, some of which involve gut-derived pathways.

In addition to the obvious role of the gut in the digestion and absorption of nutrients, the intestine and associated visceral organs, including the pancreas, liver, and visceral adipose depots, have important sensing and signaling roles in the regulation of energy homeostasis. To accomplish this role, the gut uses neural and endocrine pathways to communicate with controllers of energy balance in the hypothalamus and hindbrain. In this Review, we examine the role of the gut in energy balance

and assess the possibility that insights into gut-derived signals will stimulate previously unexplored therapeutics for obesity and other disorders of energy balance.

Integration of Peripheral Signals of Energy Balance

There is no doubt that food intake in humans is influenced by emotional factors, social cues, and learned behavior. These influences overlay highly conserved systems within the brain that sense and integrate signals reflecting overall energy stores, recent energy intake, and presence of specific classes of nutrients (Fig. 1). The hypothalamus, especially the arcuate nucleus, is relatively accessible to circulating factors and also receives inputs

from other areas of the brain. Here, signals are received that relate to total energy stores in fat and to immediate changes in energy availability, including nutrients within the gut. These two categories of signals are not exclusive, because signals relating to long-term energy stores, including insulin and leptin, can modulate responses to short-term nutritional inputs. The hypothalamus integrates these peripheral and central signals and exerts homeostatic control over food intake, levels of physical activity, basal energy expenditure, and endocrine systems, including those that determine reproductive competence (Fig. 2).

Short-term eating behavior is also controlled by the hindbrain. The nucleus of the tractus solitarius (NTS) receives input from vagus nerve afferents, whereas the area postrema is a target for circulating factors such as amylin and glucagon-like peptide 1 (GLP-1) (1). Classical studies show that when higher inputs are surgically interrupted, the hindbrain can regulate food intake in response to peripheral signals (2).

Signals of Long-Term Energy Balance

Insulin, produced by pancreatic β cells, is vital for regulating the storage of absorbed nutrients and also acts as an adiposity signal to the

Division of Endocrinology, Diabetes, and Metabolism, Beth Israel Deaconess Medical Center, Finard 202, 330 Brookline Avenue, Boston, MA 02215, USA.

*To whom correspondence should be addressed. E-mail: JFlier@bidmc.harvard.edu

brain for the regulation of energy balance (3). Mechanisms exist for transporting insulin across the blood-brain barrier and insulin receptors are expressed in appetite-controlling areas of the brain. Administration of insulin to the brain not only reduces appetite in rodents and subhuman primates but also potentiates satiety factors such as cholecystikinin (CCK). Clinically, insulin deficiency is associated with hyperphagia in uncontrolled type 1 diabetes, and intrahypothalamic administration of antibodies to insulin or neuronal disruption of insulin receptors modestly increases food intake and body weight in rodents (4).

Leptin is an adipocyte-derived factor, or adipokine, that is the dominant long-term signal informing the brain of adipose energy reserves (5). Similar to insulin, leptin is transported across the blood-brain barrier, where it binds to specific receptors on appetite-modulating neurons, most notably but not exclusively in the arcuate nucleus (6). The long form of the leptin receptor activates Janus kinase–signal transducer and activator of transcription (JAK–

STAT) signaling among several other signal transduction pathways.

Leptin-deficient *ob/ob* mice and both *db/db* mice and Zucker *fa/fa* rats that lack functional leptin receptors are hyperphagic and obese. Apart from promoting hunger, leptin deficiency reduces energy expenditure and fecundity (7). Exogenous leptin reverses obesity caused by its absence in mice and humans (8, 9); however, absolute leptin deficiency is an uncommon cause of human obesity. Instead, leptin resistance results from defects in transport across the blood-brain barrier or impaired intracellular signaling. Suppressor of cytokine signaling 3 (SOCS3) is an intracellular protein that acts to limit leptin signaling and is an important mediator of leptin resistance. Although lack of SOCS3 is embryonically lethal, mice with haploinsufficiency of SOCS3 have enhanced leptin sensitivity and are protected against diet-induced obesity and its metabolic consequences (10). Because SOCS3 also limits insulin signaling, its expression provides a potentially important point of interaction

between insulin and leptin pathways that may be important in the pathogenesis of the metabolic syndrome (11). Protein tyrosine phosphatase-1b is another factor implicated through both gain- and loss-of-function experiments as a key regulator of insulin and leptin signaling (12).

Leptin is also produced in the stomach, where it may have local paracrine functions. Its synthesis in the stomach is regulated by nutritional state and other gut hormones (13), but no physiological role of gut-derived leptin in appetite regulation has been established.

The Enteric Nervous System and Energy Balance

The enteric nervous system is implicated in every aspect of gut function. Mastication and defecation are under higher control, but the nervous system also exerts influence on gastric and pancreatic exocrine secretion, motility, blood supply, and secretion of gut hormones. Local signaling occurs within and between submucosal and myenteric plexuses, whereas afferent signals from the gut to the brain are carried in vagal and splanchnic nerve pathways. Vagal afferents respond to specific luminal chemical stimuli, physiological levels of distention or nutrients in the portal circulation, whereas splanchnic afferents convey information regarding noxious stimuli.

Vagal afferents originate from numerous areas within the abdominal viscera (Fig. 1) and different stimuli may be associated with different patterns of nerve firing. Responses to physical and chemical stimuli may be modulated by CCK, suggesting a degree of peripheral signal integration (14). In the brain, *c-fos*-like immunoreactivity (CFLI), a marker of neuronal activation, increases in the area postrema and the NTS after feeding but not sham feeding. Specific patterns of CFLI in the NTS can be induced by balloon mimicry of gastric distention (15) or duodenal infusions of nutrients. The importance of vagal afferents for meal termination is demonstrated by surgical or chemical interruptions that prevent suppression of meal size by gastric load, suppression of sham feeding by infusion of nutrients into the gut lumen, and satiety effects of exogenous CCK during real and sham feeding.

Humoral Messengers of Gut Function

The gut is a source of numerous peptides, many of which can alter appetite. These peptides have numerous targets, including gastrointestinal exocrine glands, smooth muscle, afferent nerve terminals, and the brain. Single enteroendocrine cells appear set adrift in the gut, in contrast to the archipelago of islets within the pancreas. Yet this belies the true integration of these cells into both humoral and neural systems. These highly specialized cells within the stomach, proximal small intestine, distal ileum, and colon are polar-

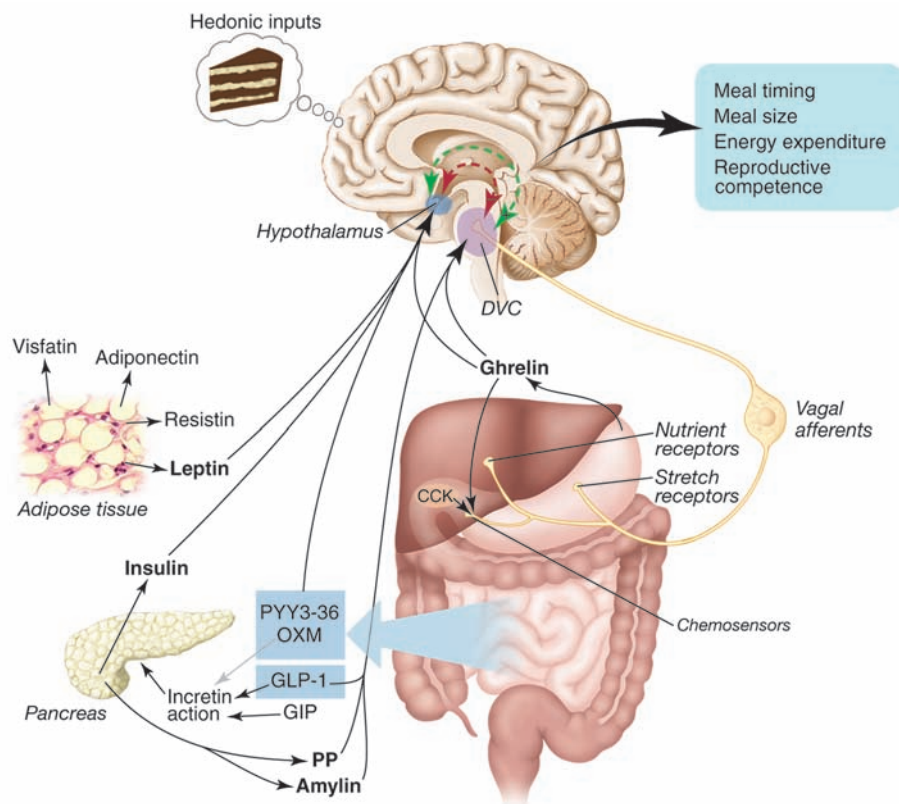


Fig. 1. The brain integrates long-term energy balance. Peripheral signals relating to long-term energy stores are produced by adipose tissue (leptin) and the pancreas (insulin). Feedback relating to recent nutritional state takes the form of absorbed nutrients, neuronal signals, and gut peptides. Neuronal pathways, primarily by way of the vagus nerve, relate information about stomach distention and chemical and hormonal milieu in the upper small bowel to the NTS within the dorsal vagal complex (DVC). Hormones released by the gut have incretin-, hunger-, and satiety-stimulating actions. The incretin hormones GLP-1, GIP, and potentially OXM improve the response of the endocrine pancreas to absorbed nutrients. GLP-1 and OXM also reduce food intake. Ghrelin is released by the stomach and stimulates appetite. Gut hormones stimulating satiety include CCK released from the gut to feedback by way of vagus nerves. OXM and PYY are released from the lower gastrointestinal tract and PP is released from the islets of Langerhans.

ized with their apical poles at the gut lumen “tasting” the nutritional milieu within the gut.

Secretion of gut hormones is regulated by receptors that sense specific chemical signals. The previously orphan G protein-coupled receptor (GPCR) GPR 120 is stimulated by free fatty acids (FFA) *in vitro* and is expressed abundantly in GLP-1-containing cells of the distal gastrointestinal tract, which release their contents in response to luminal FFA (16). Sensing of circulating FFA by β cells may occur by a similar mechanism involving the family of GPR 40 to GPR 43 to directly stimulate insulin release, complementing the incretin effect of GLP-1. GPCRs of the T2 receptor family, which sense bitter taste on the tongue, are also expressed in the stomach and duodenum and have been postulated to play a role in sensing luminal contents (17). There is also evidence that the extracellular calcium-sensing receptor is located within the gut, where it acts as a sensor for aromatic amino acids in foodstuffs (18). The fatty acid oleylethanolamide (OEA) is a ligand for peroxisome proliferator-activated receptor α (PPAR α), which specifically reduces food intake by means of a vagal mechanism (19).

Metabolic signals also play a role in stimulus-secretion coupling of enteroendocrine cells. For example, glucose stimulates secretion of GLP-1 *in vitro* by a mechanism involving adenosine 5'-triphosphate (ATP)-sensitive potassium channels, closure of which depolarizes the cell in a mechanism analogous to the β cell (20). It also appears that carbohydrate-sensing mechanisms exist that act independently of intracellular glucose metabolism (21).

Multiple peptides may be produced and packaged in secretory granules within single cell types, whereas single peptides may have numerous effects (Fig. 1). Differential processing by prohormone convertases and other posttranslational modifications, such as acylation or sulfation, further increase the repertoire of possible signaling molecules. Likewise, multiple receptor types direct distinct physiological effects that depend on the availability of the cognate receptor in a particular cell type. In addition, many gut peptides are expressed in the brain, where they function distinctly as neuromodulators. There is a complex interplay between hypothalamic and brainstem systems; hypothalamic areas such as the paraventricular nucleus have reciprocal projections with the NTS. Hence, the anorectic effects of central leptin and peripheral CCK potentiate each other. This apparent redundancy of enteroendocrine function safeguards energy intake and allows integrated responses to signals from a variety of nutrient sources.

Satiety Peptides from the Gut

CCK is the prototypical satiety hormone, produced by mucosal enteroendocrine cells of

the duodenum and jejunum and secreted in response to the presence of food within the gut lumen. Multiple biologically active forms of CCK coordinate postprandial gall bladder contraction and pancreatic secretion with gastric emptying and gut motility. Reduction in meal size is mediated by CCK₁ receptors, which preferentially bind sulfated CCK on vagal afferent neurons; hence, vagotomy reduces the effect of CCK on satiety (22). Gastric emptying is also inhibited by CCK₁ receptors on the pyloric sphincter, which may contribute to satiety. Infusion of CCK in human subjects suppresses food intake and causes earlier meal termination (23), and by contrast, infusion of a CCK₁ antagonist increases caloric intake (24).

Preproglucagon gene product yields two important satiety peptides, GLP-1 and oxyntomodulin (OXM). Both are released from L cells in response to nutrients in the form of FFA or carbohydrate. GLP-1(7–36) amide inhibits gastric acid secretion and emptying and stimulates the endocrine pancreas

with postprandial insulin release, inhibition of glucagon secretion, and, in some species, β -cell neogenesis (25, 26). Circulating GLP-1 is rapidly inactivated by the enzyme dipeptidyl peptidase IV (DPP-IV), leading to a circulating half-life of only 2 min (27). Long-acting DPP-IV-resistant GLP-1 agonists reduce food intake and induce weight loss when given peripherally to rats (28). GLP-1 receptors are present in the brain, and in rats, the blockade of endogenous GLP-1 by intracerebroventricular infusion of the specific GLP-1 antagonist exendin(9–39) increases food intake and causes obesity (29), although knockout of the GLP-1 receptor does not in mice (30). The effect of GLP-1 on human weight is inconsistent, but a meta-analysis of studies reveals that GLP-1 treatment brings about a small reduction in food intake (31).

OXM potently inhibits food intake when administered to rodents (32) and suppresses appetite in humans (33) by means of GLP-1-like receptors. Surprisingly, the areas of the brain stimulated by OXM and GLP-1 differ:

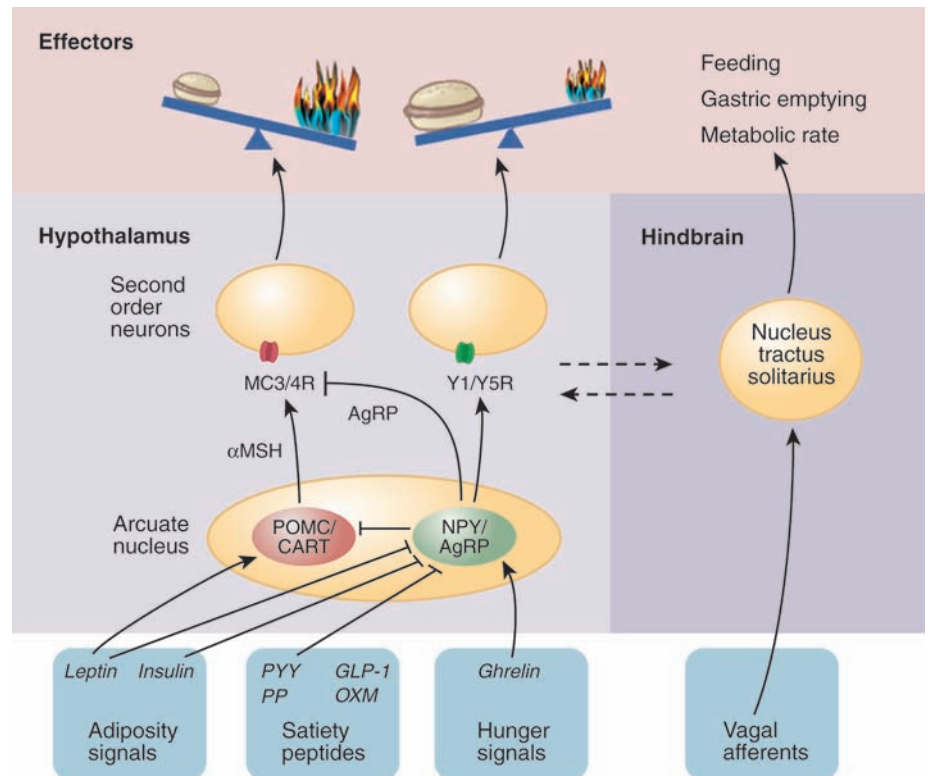


Fig. 2. Simplified representation of potential action of gut peptides on the hypothalamus. Access circulating agents into the arcuate nucleus of the hypothalamus is facilitated by a relaxed blood-brain barrier. Primary neurons in the arcuate nucleus contain multiple peptide neuromodulators. Appetite-inhibiting neurons (red) contain pro-opiomelanocortin (POMC) peptides such as α melanocyte-stimulating hormone (α MSH), which acts on melanocortin receptors (MC3 and MC4) and cocaine- and amphetamine-stimulated transcript peptide (CART), whose receptor is unknown. Appetite-stimulating neurons in the arcuate nucleus (green) contain neuropeptide Y (NPY), which acts on Y receptors (Y1 and Y5), and agouti-related peptide (AgRP), which is an antagonist of MC3/4 receptor activity. Integration of peripheral signals within the brain involves interplay between the hypothalamus and hindbrain structures including the NTS, which receives vagal afferent inputs. Inputs from the cortex, amygdala, and brainstem nuclei are integrated as well, with resultant effects on meal size and frequency, gut handling of ingested food, and energy expenditure. \rightarrow , direct stimulatory; \leftarrow , direct inhibitory; \dashrightarrow , indirect pathways.

GLP-1 activates cells in the brainstem (34) and other central autonomic control sites (35), whereas OXM-mediated increase in CFLI is limited to the arcuate nucleus (36). Moreover, injection of exendin(9–39) into the arcuate nucleus inhibits the effect of peripherally administered OXM but not GLP-1 (36), and studies examining mice deficient in the GLP-1 receptor suggest that these two peptides differentially regulate food intake and energy expenditure (37). Preproglucagon also yields GLP-2 and glucagon. Although a role of GLP-2 in appetite regulation has yet to be established, administration into the brain reduces feeding in rats, possibly by means of GLP-1 receptors. GLP-2 has not been discovered to have any effect on appetite or food intake in humans (38).

Glucose-dependent insulinotropic polypeptide (GIP) is an important incretin hormone. Similar to GLP-1, GIP is rapidly inactivated by DPP-IV. Whereas the insulinotropic effect of GIP is diminished with diabetes, GLP-1 continues to stimulate insulin secretion even in advanced stages of the disease. Release of GIP from the duodenal K cells is stimulated primarily by ingested fat such that mice fed a high-fat diet have elevated GIP levels. Notably, food intake is not affected by centrally administered GIP (39) and knockout of the receptor protects against obesity in diet-induced and *ob/ob* mice in the absence of changes in food intake by increasing energy expenditure (40). This peptide has multiple effects on adipocytes, including enhancement of insulin-stimulated glucose transport and stimulation of fatty acid synthesis and incorporation into triglycerides. Further work is needed to clarify the mechanism by which GIP promotes efficient storage of ingested energy as fat. Inhibition of this system may provide a useful anti-obesity therapeutic strategy.

The PP-fold peptide family includes neuropeptide Y (NPY), peptide YY (PYY), and pancreatic polypeptide (PP). All are produced as 36-amino acid, tyrosine-containing peptides and are recognized by a family of receptors. NPY, produced in the arcuate nucleus, is the most potent short-term stimulus for appetite. PYY is produced in enteroendocrine cells in the ileum and colon and is secreted after a meal, acting as an “ileal brake” to delay gastric emptying. In the brain, PYY(3–36) preferentially binds to presynaptic Y2 receptors within the hypothalamus to inhibit NPY neurons, release inhibition of proopiomelanocortin neurons, and depress feeding. The anorectic effect of PYY in rodents is controversial, but recent findings in nonhuman primates suggest that intramuscular administration of PYY(3–36) is associated with modestly reduced food intake (41). In humans, intravenous infusion of physiological levels of PYY(3–36) does reduce caloric intake in normal weight (42) and obese subjects (43). Malabsorptive states and diarrhea substantially increase circulating PYY.

Pancreatic polypeptide is released from specific pancreatic islet cells, primarily under nutrient control (44), to act on Y4 and Y5 receptors in the brain and peripherally to alter exocrine pancreatic and biliary function, gastric acid secretion, and gut motility. Chronic peripheral administration of PP reduces food intake in lean and obese mice (45), but central administration increases food intake. This disparity, also seen with PYY, may be caused by differential stimulation of Y4 receptors in the area postrema (which reduce food intake) and Y5 receptors expressed elsewhere in the brain (which increase food intake). In humans, PP reduces appetite and food intake without affecting gastric emptying (46).

It is clear that the field has a robust capacity to identify gut-derived factors that acutely suppress food intake in one or more experimental paradigms. Although interest in this area continues to grow, the true challenge will be to integrate the action of these multiple gut hormones. Both genetic and pharmacological approaches will be necessary to elucidate the relative importance of these numerous satiety factors to physiology, pathology, and potential therapeutics.

A Gut Peptide That Stimulates Hunger

Ghrelin is a 28-amino acid acylated hormone with appetite-stimulating and growth hormone-releasing activities mediated by the growth hormone secretagogue receptor (47). Cells that synthesize ghrelin are located throughout the gastrointestinal tract, at highest density in the fundus of the stomach. Plasma levels of ghrelin rise during fasting and immediately before meals and fall within an hour of food intake, suggesting a role in meal initiation (48).

In the arcuate nucleus of the hypothalamus, ghrelin activates neurons expressing NPY (49). Stimulation of gastric vagal afferents (50) and direct ghrelin action on the dorsal vagal complex (51) also appear to mediate ghrelin signaling. However, the role of ghrelin in obesity is open to question, as ghrelin levels tend to be low in obese humans, only increasing after dietary weight loss (52), and initial reports suggest that deletion of ghrelin (53) or its receptor (54) does not impair food intake or substantially alter body weight. Given that intravenous administration of ghrelin increases appetite and food intake in volunteers of normal weight and increases food intake of patients with cancer-related anorexia by over 30% (55), ghrelin or the activation of its receptor may find a use in the treatment of anorexia.

Loss of appetite and cachexia may occur in many gastrointestinal disorders, including hepatopancreaticobiliary disorders, celiac disease, gastrointestinal infections and infestations, radiation enteritis, and intestinal resection. Changes in the endocrine milieu have been

reported in malabsorptive states (56). The future availability of peptide and small molecule antagonists of gut-peptide receptors will permit testing the hypothesis that such appetite loss may be due to altered secretion of gut-derived satiety factors.

Other Peptides of Visceral Origin Potentially Linked to Energy Balance

Amylin (islet amyloid polypeptide) is a 37-amino acid peptide cosecreted with insulin by pancreatic β cells (57). In animal studies, synthetic amylin analogs delay gastric emptying and decrease food intake (58), an effect mediated by the area postrema in rats. Studies in humans involving an amylin analog, pramlintide, have produced weight loss in diabetic populations (59). The bombesin homologs, gastrin-releasing peptide and neuromedin B, reduce meal size in several species, including humans (60).

Enterostatin is a pentapeptide cleaved from procolipase released by the exocrine pancreas. Peripheral and central administration reduce food intake in rats and alter food preference away from fatty foodstuffs, but in humans, recent metabolic studies have failed to show an effect of oral enterostatin on food intake, appetite, energy expenditure, or body weight (61).

A Special Role for Visceral Fat in Obesity and Energy Balance?

Deposition of fat within the abdomen, so-called visceral adiposity, confers greater risk of metabolic and cardiovascular complications than does adipose accumulation elsewhere. The mechanistic basis for this association has stimulated much interest. Whereas adipose tissue was viewed as a means of storage and release of energy in response to shifts between fed and starved states, the adipocyte is now recognized as a bona fide endocrine cell. Adipocyte hormones influence appetite, glucose homeostasis, vascular function, and even reproductive competence, among other functions (62). It is likely that adiposity within the abdomen is metabolically harmful both because of its unique anatomical relation to the hepatic portal circulation and because of the specific endocrine features of this adipose depot. Adiponectin is an adipokine with insulin-sensitizing and anti-inflammatory actions that is suppressed in obesity in parallel to reduced insulin sensitivity (63). By contrast, resistin, a 108-amino acid peptide hormone that is expressed in adipocytes in rodents and in macrophages in humans is induced in obesity and leads to insulin resistance (64). The induction of resistin by cytokines may be a link between obesity and inflammatory states resulting in insulin resistance (65). Visfatin is a newly discovered adipokine expressed at high levels in visceral fat that has the notable property of activating the insulin receptor by bind-

ing at a site distinct from that recognizing insulin. Visfatin stimulates glucose uptake by adipocyte and muscle cells in vitro and decreases blood glucose levels in mice (66). It is a paradox that an insulinomimetic factor is produced by visceral fat in a state of insulin resistance. Further studies will be required to elucidate a physiologic role for visfatin and whether resistance to its action is seen in insulin-resistant states.

Obese Zucker rats overexpress the glucocorticoid reactivating enzyme 11 β -hydroxysteroid dehydrogenase 1 (11 β -HSD1) in adipose depots, presenting the possibility of “Cushing’s disease of the omentum” resulting from local overproduction of cortisol in humans. Mice overexpressing 11 β -HSD1 in fat are hyperphagic, have visceral obesity, and develop insulin-resistant diabetes and hypertension (67). Conversely, mice with global deletion of 11 β -HSD1 are protected from diet-induced obesity and related hyperglycemia. In humans, increased 11 β -HSD1 expression and activity has been reported in adipose tissue in some but not all studies.

Potential Gut Mechanisms in Obesity Therapeutics

The expanding understanding of gut endocrinology has produced a number of potentially fruitful avenues for the development of obesity therapies. The traditional approaches of caloric restriction, exercise, and behavioral therapies can each produce substantial weight loss, but in the majority of people this is not sustained. Two pharmacological agents are currently licensed for weight loss. Orlistat interferes with fatty acid hydrolysis and uptake by the gut through inhibition of pancreatic lipases. Sibutramine, a centrally acting norepinephrine and serotonin reuptake inhibitor, reduces appetite and may increase energy expenditure. Both produce only modest weight loss and may have unwelcome side effects.

Regulation of energy balance presents numerous potential targets for intervention in both the periphery and the central nervous system. Leptin replacement is effective in the rare cases of human leptin deficiency (9), but leptin resistance limits its utility in ordinary obesity. Increasing leptin action by promoting its transport into the brain or by antagonizing inhibitors of leptin signaling pathways might be effective, but the relevant pharmaceutical targets have proven challenging. Axokine, a reengineered recombinant human ciliary neurotrophic factor, acts through leptin-like pathways in the hypothalamus. Although effective in animal models, human obesity trials were limited by neutralizing antibodies (68).

Rimonabant is a compound that acts both centrally and peripherally to antagonize the cannabinoid-1 (CB1) receptors that play a role in energy balance. Recently reported phase III

clinical trials show that 2-year treatment with rimonabant reduced weight, reduced abdominal fat, and improved cardiovascular risk factors (69). The first in a new class of pharmaceutical agents, rimonabant is promising as an anti-obesity therapy, but its clinical value compared with that of existing therapies must await results of future investigations. Antagonists of the receptor for melanin-concentrating hormone and agonists for the melanocortin 4 receptor might be efficacious and are being pursued.

The favorable action of GLP-1 on both insulin secretion and energy balance makes it an attractive candidate for drug development. Exendin-4 is a 39-amino acid peptide originally isolated from the saliva of the Gila Monster that resists degradation by DPP-IV while retaining GLP-1-like effects on glucose metabolism and food intake (70). Activity of GLP-1 is prolonged by conjugation to albumin (liraglutide) or inhibition of DPP-IV. An amylin analog (pramlintide) causes weight

loss in diabetic cohorts, but its efficacy in the general population is uncertain. A number of formulations of PYY(3–36) are currently under development as obesity therapeutics, although effective small-molecule mimics are lacking. Stimulation of endogenous GLP-1 and PYY(3–36) secretion by specific L cell secretagogues is a promising avenue that remains to be exploited. Ghrelin may ameliorate anorexia (55), but the efficacy of ghrelin antagonists for treatment of obesity remains unproven. Whether energy balance will be improved in humans by inhibition of 11 β -HSD1 or alternatively activation of PPAR α , as suggested by studies of OEA action, will await the results of clinical trials.

Obesity Surgery

It has been estimated that 15,000,000 adults in the United States meet current guidelines for surgical intervention to treat obesity (71). Once a last resort, surgery is increasing rap-

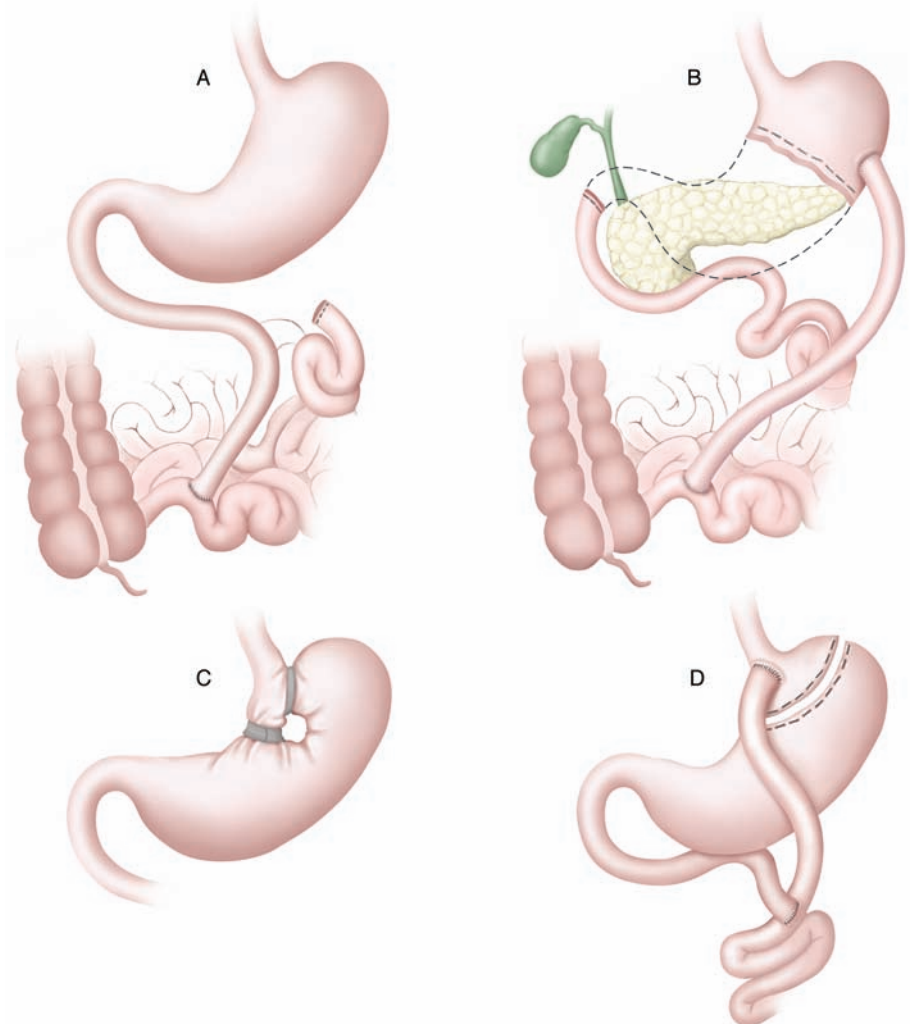


Fig. 3. Surgical procedures have developed from interventions causing gross malabsorption, such as jejunioileal bypass (A), and restriction and malabsorption, including biliopancreatic diversion (B). Currently, popular procedures include restriction of gastric volume with vertical banded gastroplasty (C) and the RYGB (D). The latter is free of malabsorption after an initial phase of adjustment and subsequently produces an advantageous gut hormonal milieu.

idly as a means of weight control, from approximately 15,000 annual procedures in the early 1990s to over 100,000 operations in the United States in 2003 (72). Bariatric surgery can achieve substantial and long-term weight loss and can improve or in some cases cure diabetes, hyperlipidemia, hypertension, and obstructive sleep apnea. Jejunoileal bypass was the original widely accepted bariatric procedure (Fig. 3) but can cause malabsorption, hepatic failure, and nephrolithiasis. Biliopancreatic diversion and duodenal switch restrict gastric volume and avoid bacterial overgrowth in the bypassed small bowel, but Roux-en-Y gastric bypass (RYGB) is the most commonly performed procedure in the United States. Its success stems from limiting the size of the gastric pouch, a small amount of malabsorption, and effects on hormonal signals from the gut, which may be critical to the efficacy of this procedure. Diabetes is rapidly ameliorated after RYGB and glycemic improvements often precede weight loss, supporting the view that changes in the gut hormonal milieu may be involved. An effect of surgery to increase PYY and GLP-1 levels has been reported (73). A postoperative fall or a failure of ghrelin levels to rise after surgery, as it does after weight loss due to food restriction, has been observed (52, 73), but proof that ghrelin suppression accounts for reduced appetite after RYGB awaits experiments in which ghrelin is replaced in such patients. A second procedure gaining wide application is adjustable gastric banding. While this surgery is less complex, the results are somewhat less impressive than RYGB, and the effect of this procedure on gut endocrine factors is less explored. Removal of omental fat during gastric surgery for obesity may improve glucose homeostasis (74), and future studies of this approach are warranted.

In gastric pacing, electrical stimulation of the antrum of the stomach causes reverse peristalsis and delayed gastric emptying. A U.S. trial of this procedure revealed that up to 40% of excess weight could be lost 2 years after treatment without complications (75). Similarly, direct pyloric stimulation reduces gastric emptying and food intake in an animal model (76). However, it is not yet known how these interventions work. A limited study showed that gastric pacing was associated with a decrease in CCK, somatostatin, and GLP-1 levels (77) and a mechanistic role for stimulation of vagal afferents has also been propounded. There is some support for this idea in that direct vagal stimulation is known to lead to weight loss in animal models (78).

Conclusion and Perspective

A new understanding of the role of the gut in obesity and energy balance has recently developed. The list of peptide hormones emanating from the gastrointestinal system and

influencing energy balance continues to grow, and it seems likely that additional gut hormones will be identified. Although loss-of-function studies indicate a high degree of redundancy, this does not preclude the potential efficacy of obesity-regulating drugs acting on these targets. Indeed, the likely introduction of GLP-1 agonists as diabetes treatments with weight loss potential heralds a new era of anti-obesity therapy. Moreover, the apparent importance of alterations in the gut hormonal milieu caused by surgical intervention on the gastrointestinal tract could lead to new approaches to surgery or devices. Of course, many unanswered questions remain. Among these are the possible roles of gut pathways in the genetic etiology of obesity and diabetes, a better understanding of the receptors and signals that sense specific nutrients in the gut, and a better understanding of the hierarchy and interactions between different gut signals and between gut signals and those related to long-term energy stores, such as leptin.

Perhaps it is fortuitous that the obesity epidemic has been paralleled by a rapid advance in understanding of mechanisms that control energy balance. Interventions that modulate gut-related satiety signals either pharmacologically, surgically, or electrically may offer a new armamentarium in our efforts to curb this threat to human health.

References and Notes

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