



Roles of the Gut in Glucose Homeostasis

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The gastrointestinal tract plays a major role in the regulation of postprandial glucose profiles. Gastric emptying is a highly regulated process, which normally ensures a limited and fairly constant delivery of nutrients and glucose to the proximal gut. The subsequent digestion and absorption of nutrients are associated with the release of a set of hormones that feeds back to regulate subsequent gastric emptying and regulates the release of insulin, resulting in downregulation of hepatic glucose production and deposition of glucose in insulin-sensitive tissues. These remarkable mechanisms normally keep postprandial glucose excursions low, regardless of the load of glucose ingested. When the regulation of emptying is perturbed (e.g., pyloroplasty, gastric sleeve or gastric bypass operation), postprandial glycemia may reach high levels, sometimes followed by profound hypoglycemia. This article discusses the underlying mechanisms.

THE INCRETIN EFFECT

One of the ways to illustrate the role of the gut in glucose homeostasis is to compare the fate of glucose that has been administered orally or infused intravenously. If the same amount of glucose is given, the results may not be particularly remarkable, at least not with relatively small amounts of glucose (25 g or roughly one-half the amount of sugar as in a can of soda). The amount of insulin secreted (estimated from C-peptide responses) may be almost the same, and any differences in peripheral insulin concentrations could be interpreted as indicative of differences in hepatic insulin clearance (1). However, if the intravenous glucose infusion is adjusted so that the resulting plasma glucose concentrations are identical to those after oral or small intestinal administration of glucose, substantially more insulin is secreted with oral or enteral administration, a phenomenon known as the incretin effect (2). The incretin effect is usually interpreted to indicate secretion of insulinotropic substances (incretin hormones) from the gut (3). Another way of looking at these experiments is to compare the amounts of infused glucose required to obtain identical circulating glucose concentrations: for 25 g given orally, only about 19 g need to be infused intravenously (4). This method shows that oral administration activates a mechanism that clears 6 of the 25 g of glucose from the circulation and is sometimes referred to as gastrointestinal induced glucose disposal (GIGD), which amounts to 24% of the oral dose in this case. With larger amounts of glucose, GIGD becomes increasingly prominent, and with 100 g of glucose infusion, GIGD is responsible, in healthy subjects, for removing about 80% of the glucose administered orally (4), which is equivalent to ~20 g left in the circulation, comparable to the amount required to mimic the 25-g oral dose. Indeed, the plasma glucose excursions after 25, 50, 100, and up to 125 g of oral glucose (5) are similar, regardless of the dose, whereas excursions would be hugely different if similar amounts were infused intravenously. GIGD, therefore, minimizes blood glucose excursions very efficiently

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so that they are maintained at a relatively constant level regardless of the amount of glucose ingested. In patients with type 2 diabetes, things are very different: in these individuals, GIGD is greatly reduced, even to as low as 0% (5).

What mechanisms underlie GIGD? In healthy people, increasing oral glucose loads are associated with dose-related increases in insulin secretion, and this is a major mechanism because in patients with insulin-deficient type 1 diabetes, the GIGD is usually close to zero (6). Therefore, it may be concluded that the incretin effect (the amplification of insulin secretion by gastrointestinal factors) is a major mechanism for normal glucose tolerance. Strictly speaking, the incretin effect refers to enhanced insulin secretion in response to oral or enteral glucose, but a similar enhancement of insulin secretion is also observed after oral intake of both fat and protein (7). Thus, although a formal comparison between oral and intravenous administration cannot be made easily for mixed meals, it may be assumed that an incretin effect plays an important role in postprandial glucose homeostasis in general. As will be detailed later, the incretin effect is due to hormones secreted from the gut epithelium, the most important ones being glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) (8). In agreement with the loss of GIGD, the incretin effect is also greatly reduced or entirely missing in patients with diabetes (9).

Recently, the existence of a dectetin, a duodenal hormone that inhibits insulin secretion, has been proposed based on studies in *Drosophila* flies. The human counterpart is supposed to be the peptide neuromedin U, which may inhibit insulin secretion (10). However, more studies are required to support this mechanism, which might be relevant for the metabolic effects of gastric bypass operations.

MECHANISMS REGULATING GLUCOSE EXCURSION AFTER ORAL INTAKE

Anticipatory Events

The sight, smell, taste, and sensory impulses generated by food presentation, mastication, and swallowing of an appetizing meal undoubtedly result in excitatory signals to the gastrointestinal tract (10). This has been studied in detail in relation to gastric acid secretion, where

sham feeding (intake and chewing of an appetizing meal that is prevented from entering the stomach, typically by spitting it out) elicits ~65% of maximal gastric acid secretion (11). In experimental animals, a substantial cephalic phase insulin response can often be demonstrated, but in humans this is less apparent. In fact, in a recent study where glucose levels were clamped at a permissive level (6 mmol/L [108 mg/dL]), an insulin response could not be demonstrated, whereas the secretion of pancreatic polypeptide (known to strongly depend on vagal efferent activity [12]) was greatly increased (13). Similarly, demonstrating any clear cephalic phase for the secretion of gut hormones involved in the incretin effect has been difficult (13), and although it is easy to demonstrate experimentally an effect of the efferent vagus nerves on the secretion of gastric and pancreatic hormones (14) (but not gut hormones [15]), this mechanism is not clearly activated in the initial response to meals.

Roles of the Stomach

Before nutrients are absorbed into the bloodstream, they normally are retained for some time in the stomach. The rate of gastric emptying highly depends on the composition and macronutrient content of a meal. Fundamental differences exist in patterns of gastric emptying of liquids and solids; the emptying of digestible solid components of a meal comprises an initial lag phase of 20–40 min, when solids are ground into small particles, followed by an emptying phase, which approximates an overall linear pattern (16). In contrast, low-nutrient liquids empty in a monoexponential pattern without a significant lag phase, which changes to a linear pattern as nutrient density increases. Although liquids and solids are ingested concurrently, as in a mixed meal, liquids empty preferentially, so that ~80% is emptied before solids. The rate of gastric emptying usually is relatively unaffected by the volume of the meal. Accordingly, meals with a higher nutrient content take longer to empty, but they empty at a similar rate when expressed as kilocalories per minute (17). Therefore, in experiments with increasing amounts of glucose (25–75–125 g) ingested in the same volume, peak absorption estimated from the liquid phase marker acetaminophen was delayed from 30 to 90 and 180 min, respectively

(5). It is not widely appreciated that a substantial interindividual variation exists in gastric emptying; in healthy persons, this is usually 1–4 kcal/min (18).

The rate of gastric emptying is now recognized to be a major determinant of not only the early but also the overall postprandial glucose excursion in healthy individuals and those with type 2 diabetes (19,20). Consistent with the maintenance of relatively constant postprandial glucose levels, irrespective of the increasing glucose load, the three glucose loads in the study referred to previously (5) were also associated with comparable initial rises of incretin hormones, which were then maintained according to the dose of glucose (very briefly for the low dose, but for up to 3 h after the highest dose) (Fig. 1). In other words, the emptying of nutrients from the stomach is adjusted so that the entry rate of the meal into the small intestine is relatively constant and results in an incretin hormone response that persists for as long as nutrients are still entering the gut.

Studies involving direct infusion of glucose into the small intestine at rates within the normal range of gastric emptying have provided important insights into the relationships of the glycemic, GLP-1, and GIP responses with the rate and site of glucose entry into the small intestine (22), as discussed in REGULATION OF GASTRIC EMPTYING. These studies demonstrate that the relationship of glycemia with small intestinal glucose delivery is nonlinear. Both the viscosity and the physical state of a meal influence the meal's gastric handling, with increasing viscosity (as seen for various fermented milk products) directly slowing emptying (23). The physical state of some nutrients may change upon entry into the stomach. Emulsified lipids (milk, mayonnaise), for instance, rapidly coalesce to form a lipid phase, which retards their emptying (depending on posture [24]). Proteins, depending on their rate of initial pepsin-mediated gastric digestion and reaction to gastric acid, may coagulate and form solids (as seen for caseins), which again influences their digestion and emptying (25).

Regulation of Gastric Emptying

The mechanisms that regulate gastric emptying are extremely complex, involving gastric and intestinal hormones as well as long and short reflexes. In

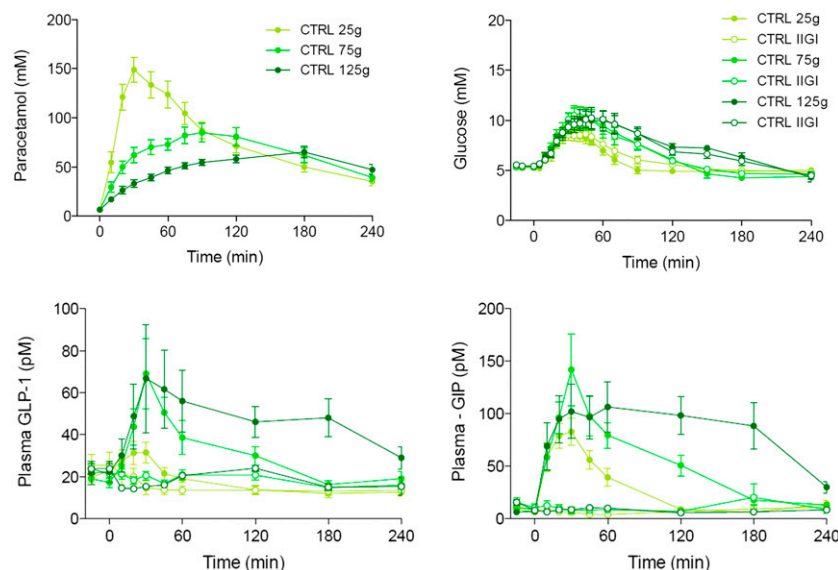


Figure 1—Gastric emptying (paracetamol absorption) and its impact on postprandial glucose and incretin hormone levels in healthy volunteers after oral intake of 25, 75, and 125 g of glucose. Insulin levels (not shown) increased in proportion to emptying rates. See text for further analysis. CTRL, control; IIGI, isoglycemic intravenous glucose infusion. Modified from Bagger et al. (5).

general, the dominant mechanisms that regulate gastric emptying result from the interaction of nutrients with the small intestine rather than intragastric mechanisms. Small intestinal feedback is mediated by the digestion products of carbohydrates, fats, and proteins and is regulated by both the length and the region of small intestinal exposure to nutrients (26). Normal gastric emptying depends on coordination of the contractile activity of the proximal stomach, antrum, pylorus, and upper small intestine through the extrinsic and intrinsic nervous systems as well as through neurohumoral pathways. Gastric receptive relaxation (and subsequent accommodation), which is a vagal reflex, is important because it allows meals to enter the stomach without increasing the wall tension substantially, allowing symptom-free accommodation of meals of greatly varying sizes.

Pyloric motor activity is highly regulated by branches of the vagus nerve (the nerve of Latarjet) in a system of short reflexes and hormonal mechanisms that are stimulated by the entry of nutrients and gastric fluids (e.g., acid) into the duodenum. Thus, the introduction of acid into the duodenum may halt gastric emptying altogether while exciting duodenal propulsive motility (27). Ghrelin, secreted from the stomach, can accelerate gastric emptying (28), whereas secretin,

cholecystokinin (CCK), and somatostatin, secreted from the proximal small intestine, all inhibit both gastric secretion and gastric emptying. Gastric emptying may also be influenced by hormones from the more distal small intestine, including GLP-1 and peptide YY (PYY) (both the intact hormone PYY 1-36 and the 3-36 metabolite), which are powerful inhibitors of both secretion and motility (29).

Any interference with these mechanisms has the potential to influence exposure to and, hence, rate of absorption of nutrients from the small intestine and, ultimately, increases in concentrations of glucose and other nutrients in the bloodstream. The elimination or impairment of these powerful mechanisms accounts for many of the changes observed after bariatric procedures, such as Roux-en-Y gastric bypass and sleeve gastrectomy.

Digestion

Although glucose as a monosaccharide is not a major constituent of the normal diet, it is a major component of the carbohydrates we ingest in the form of starch, lactose, and sucrose. For these nutrients, enzymatic cleavage is required. Salivary amylase is believed to contribute minimally to the digestion of carbohydrates, which therefore primarily depends on pancreatic amylase along with brush-border lactase, maltase, isomaltase, and sucrase activities. These

mechanisms normally do not appear to be rate limiting for glucose absorption; for example, sucrose seems to be digested and absorbed at a rate proportional to its load in the small intestine (30). For many complex carbohydrates, however, enzymatic digestion (and as determining factors for digestion, small intestinal propulsive activity and segmenting motor activity) is far more complex. Under normal circumstances, a substantial amount of dietary carbohydrate escapes absorption in the small intestine and is presented to the colon for bacterial fermentation, even in humans (31). The colon can absorb glucose, but this capability is probably rarely exploited because fermentation proceeds rapidly. An outcome of fermentation is the production of volatile fatty acids (acetate, propionate, and butyrate), which are important metabolic products for colonic metabolism, but these fatty acids are also absorbed and may be used for combustion and hepatic gluconeogenesis (particularly propionate) (32). Gluconeogenesis might also occur in the intestine, but its contribution to glucose homeostasis in humans is unknown. Of note, increased intestinal gluconeogenesis was proposed to account for some of the changes in glucose homeostasis after gastric bypass in rats (33) (i.e., the increased intestinal gluconeogenesis would inhibit hepatic glucose production). On the other hand, increased glucose combustion within the hypertrophied gut after gastric bypass in rodents has also been suggested as an explanation (34); however, glucose kinetics after bypass in humans do not seem to be consistent with this hypothesis (21). Lactase insufficiency is, of course, limiting for lactose absorption in many adults, and the extent to which this may represent a problem in bariatric/metabolic surgery is well worth study.

Absorption and Deposition

The next step in intestinal glucose handling after digestion is transport through the sodium-glucose cotransporter 1 (SGLT1). Fructose is transported through GLUT-5 and partly metabolized in the intestine before reaching the liver for further metabolism and regulation of its glucose production. Fructose, therefore, also influences glucose metabolism, but nothing is known about its specific role after bariatric/metabolic surgery (35).

Glucose transport through SGLT1 occurs in cotransport with two molecules of sodium and is very efficient. Some glucose absorption might also occur after translocation of GLUT-2 to the apical membrane (36). At any rate, there is normally very little malabsorption of glucose. The absolute rate of glucose absorption depends on the rate of exposure of the small intestine to glucose (as discussed previously), the region and length of small intestine exposed, and the number of functional enterocytes and their expression of glucose transporters (and, therefore, the availability of luminal sodium ions). Moreover, small intestinal motility and the flow of luminal content are determinants of glucose absorption, and these are potential targets for pharmacological manipulation (37). Bariatric/metabolic surgery is believed to induce adaptive growth, particularly of the alimentary limb, and to involve the common limb (38), which facilitates absorption. Absorption after surgery is extremely rapid, and complete absorption is obtained more rapidly than in individuals who do not undergo this surgery (Fig. 2) (21). Even when rapid emptying of glucose from the gastric pouch is bypassed by infusing at a controlled rate directly into the small intestine, absorption of glucose is more rapid than in healthy control subjects (39).

The rapid entry of nutrients from the gastric pouch after bypass surgery (estimated at ~100 kcal/min for a glucose solution [39]) often is associated with a constellation of symptoms collectively referred to as dumping, including feelings of weakness, desire to lie down, impaired consciousness, sweating, palpitations, and tachycardia. The syndrome is well known from other gastric operations with accelerated gastric emptying (impaired retention) (40), but understanding of the pathophysiology is still evolving (41). An increased osmotic load in the small intestine results in water accumulation in the gut lumen through a leaky proximal intestinal epithelium and potentiates the usual increase in intestinal blood flow in response to nutrients (42), overwhelming the capacity of the sympathetic nervous system to compensate and leading to a fall in blood pressure. A second important element is the exaggerated secretion of gut peptides, including GLP-1, triggered by the rapid nutrient entry into the small

intestine, leading to a spike in insulin secretion and subsequent hypoglycemia (43), as discussed next. After Roux-en-Y gastric bypass, most patients rapidly identify nutrients that will cause dumping (e.g., soft ice or large amounts of sugar-sweetened drinks).

The increase in intestinal blood flow during meal ingestion is also important for the resulting transport of glucose to the systemic circulation. Part of the glucose is metabolized and used for combustion in the gut (as mentioned previously, this has been proposed to represent one of the mechanisms for improved glucose tolerance after bypass [34]), but the majority passes to the liver where a proportion is taken up and used for combustion or stored as glycogen. These processes are highly regulated by insulin. The liver is the main target for insulin action (44), and postprandially, hepatic glucose production is effectively shut down, whereas hepatic glucose uptake is enhanced (21). However, a considerable part of the absorbed glucose passes through the liver so that there is a rise in plasma glucose concentration. Simultaneously, glucose uptake in tissues expressing glucose transporters (GLUT-1 to -4) increases as a function of the increased glucose concentration (mass action) (45). With rising insulin concentrations and increased insulin-stimulated translocation of GLUT-4, peripheral glucose transport is further enhanced. Thus, after gastric bypass surgery, glucose deposition is greatly accelerated and may overshoot the rate of absorption whereby glucose concentrations fall below fasting levels (21). Indeed, in most patients who undergo bypass surgery, there is a pronounced decrease in plasma glucose concentrations after a glucose load, and in some, there is significant hypoglycemia (46), which may worsen as insulin resistance diminishes with progressive weight loss. After glucose ingestion, secretion of glucagon normally falls, which, together with rising glucose and insulin concentrations, accounts for the decrease in hepatic glucose production (which in the fasting state is maintained by the basal levels of glucagon reaching the liver). After gastric bypass, meal or glucose ingestion is associated with an increase in peripheral glucagon concentrations (47), which would be expected to result in failure of the usual suppression of hepatic glucose production. The consequences of the

paradoxical increase in glucagon for overall glucose tolerance have not yet been evaluated, although they could be significant.

The Liver and Neural Regulation

We have discussed the paramount importance of the gastrointestinal tract for postprandial glucose dynamics as well as the importance of retention in the stomach, small intestinal motility, enzymatic digestion, and transmucosal glucose transport capacity. The importance of the regulation of hepatic glucose production and uptake has also been mentioned, and how the pancreatic hormones insulin and glucagon regulate this has been outlined. We next describe how the gut regulates insulin and glucagon secretion, but before doing so, we may ask to what extent hepatic glucose handling is influenced by the nervous system. The human liver has both vagal and sympathetic fibers. The sympathetic system is known to enhance hepatic glucose production through the actions of the catecholamines on glycogenolysis, whereas the actions of the vagus are more unclear. The activity of the sympathetic system is regulated by the hypothalamus as a part of the stress reaction but may also receive input from the gut. Glucose-sensitive nerve fibers in the intestinal mucosa and the hepatic portal system send impulses to the brain (48). These signals must run in the afferent vagus or the sensory sympathetic neurons entering the medulla through the dorsal horns activating ascending tracts to the brain, but evidence suggests that the vagal mechanisms predominate (49). These mechanisms have been studied mainly in animals, and their importance in humans is unknown. Several decades ago, an established therapy for duodenal ulcer disease was truncal vagotomy together with a gastric drainage procedure (usually pyloroplasty) to mitigate the motor consequences of vagotomy (gastric stasis) (50). Most patients tolerated this procedure well, but their glucose metabolism was altered, with increased but short-lived postprandial rises and an exaggerated overshoot after glucose challenge, but these were probably consequences of the drainage procedure (51). Fasting glucose was little affected. The relevance of both efferent and afferent impulses for normal glucose tolerance cannot be determined from these experiments. Central nervous

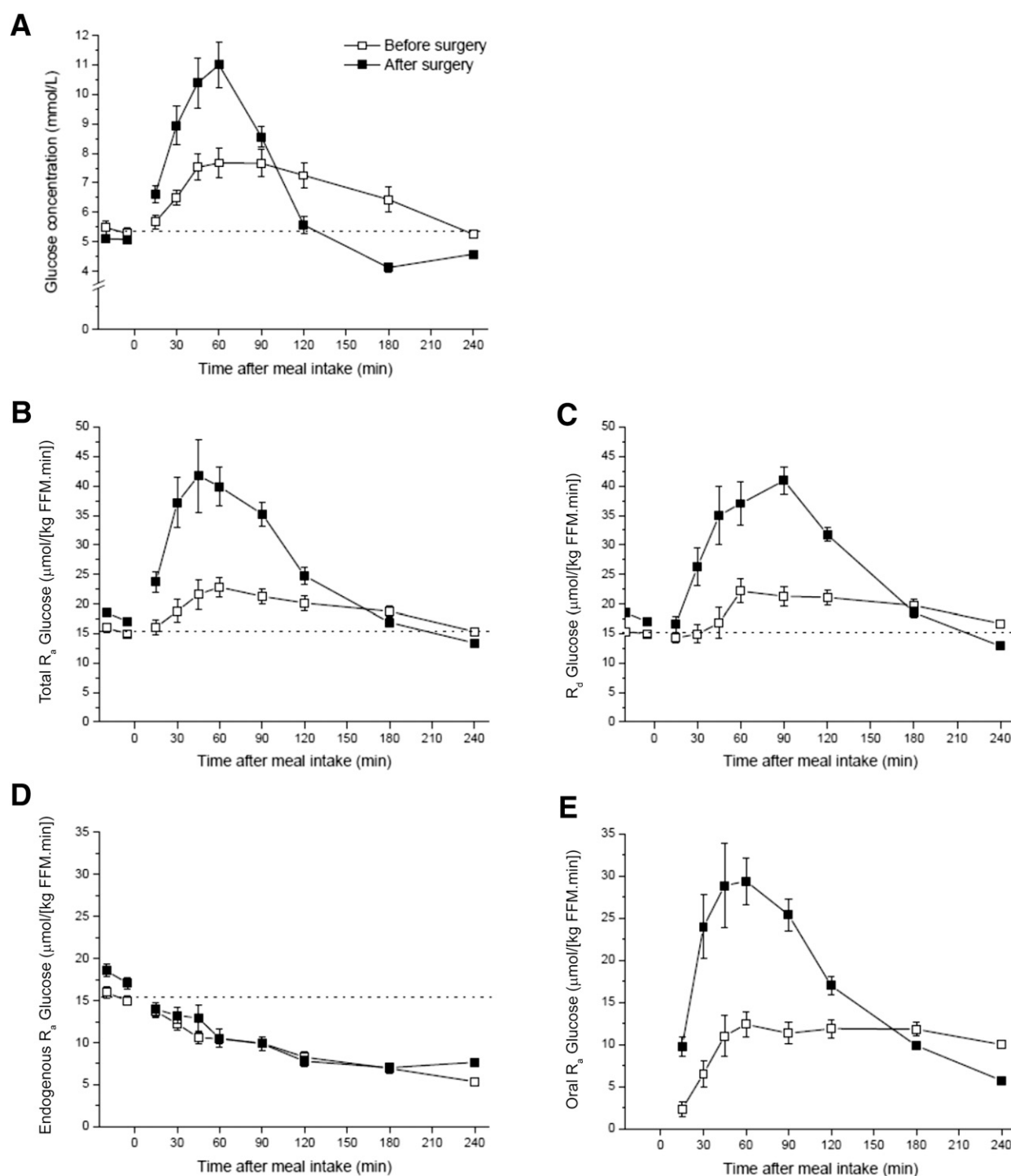


Figure 2—Plasma glucose concentration (A), total glucose rate of appearance (R_a) in (B) and rate of disappearance (R_d) from (C) the systemic circulation and endogenous (D) and oral (E) R_a in the systemic circulation before and ~3 months after Roux-en-Y gastric bypass. The dotted lines mark preoperative basal levels. A primed continuous infusion of [6,6- d_2]glucose was given for 2 h before determination of steady-state glucose and tracer enrichment, and then a mixed meal (200 mL [394 kcal] carbohydrate 50%, protein 15%, fat 35%) consisting of glucose (48.4 + 1.6 g [U - ^{13}C]glucose), rapeseed oil (14.1 g), and casein protein (15.2 g) was consumed slowly over 30 min (21). FFM, fat-free mass.

system regulation of hepatic glucose production is probably mainly exerted through the sympathetic innervation reaching the liver, which may be activated through glucose-sensitive hypothalamic neurons (52); however, the

role of these systems for normal glucose homeostasis in humans is not known. Intestinal nutrient sensing by a variety of mechanisms has been proposed to regulate hepatic glucose production through a reflex pathway comprising

ascending vagal afferents signaling to hypothalamic nuclei, which in turn regulate hepatic glucose production (53). Major intestinal signals were believed to be CCK and leptin derived from the stomach (54,55), but the inconspicuous effects of

CCK in human glucoregulation (56) and the limited survival of leptin in the lumen of the gastrointestinal tract seem to limit the importance of these signals. Although afferent sensory mechanisms undoubtedly play an important role in the regulation of food intake (57), the experimental support for a similar reflex mechanism to regulate hepatic glucose production in larger mammals and humans is lacking (44).

Gut Endocrine Regulation of Glucose Metabolism

In addition to regulating postprandial blood glucose levels by controlling the gastric emptying rate, the small intestine modulates appetite and pancreatic hormone secretion through the release of gut hormones. These in turn have profound effects on peripheral metabolism. Gut endocrine control of appetite is mediated by hormones such as GLP-1, PYY, and CCK, which are produced by enteroendocrine cells scattered within the intestinal epithelium. The anorexic action of these hormones is probably mediated through at least two distinct pathways: altered activity of intestinal sensory nerves (particularly the afferent vagus) relayed to the hypothalamus through the brain stem and direct sensing of circulating gut hormone levels at the level of the brain stem and/or hypothalamus (58). By controlling appetite and energy intake, gut hormones influence the size of adipose tissue stores, which are the major determinants of peripheral insulin sensitivity. Gut hormone control of pancreatic hormone secretion underlies the incretin effect described previously and is largely mediated by circulating GIP and GLP-1. Both these hormones are produced by enteroendocrine cells, but whereas GIP is predominantly found in K cells located in the duodenum and proximal small intestine, GLP-1-producing L cells are found in much higher density in the jejunum, ileum, and colon (59). K and L cells respond to nutrient absorption rates and are able to sense a variety of digested nutritional components, including carbohydrates, fats, and proteins (60). By responding to nutrient absorption rather than the mere presence of nutrients in the gut lumen, increased gut hormone levels provide a meaningful humoral signal indicating the arrival of nutrients from the gut into the bloodstream. Because

GIP-producing K cells are located in the duodenum, their exposure to nutrients and, therefore, secretion rate highly depend on the rate of gastric emptying (5). The more distal location of L cells adds complexity to the postprandial profile of GLP-1 concentrations (61). An early initial peak in GLP-1 secretion triggered by the appearance of nutrients in the jejunum is associated with slowing of gastric emptying, and at lower nutrient flow rates, the duodenal absorption capacity can keep up with supply, so the overspill of nutrients into the distal gut is reduced (62). In studies where glucose was infused directly into the duodenum, plasma concentrations of GIP increased in approximately linear fashion with increasing rates of infusion. In contrast, there was minimal GLP-1 release below a threshold of 1–2 kcal/min (62) but a substantial GLP-1 response at 3–4 kcal/min (22), suggesting that which of the incretins is predominant depends on the rate of gastric emptying. Inconsistency exists between studies about whether incretin secretion is altered in obesity or type 2 diabetes compared with health, and although decreases in GLP-1 secretion usually can be demonstrated (63), no substantial differences, particularly in the early postprandial phase, have been found (64). However, individuals with morbid obesity manifest accelerated glucose absorption from the proximal small intestine, with a corresponding shift toward greater secretion of GIP and less of GLP-1 than seen in lean individuals (65).

Enteroendocrine cells detect rates of nutrient absorption through a variety of mechanisms. Mirroring SGLT1-mediated glucose absorption across the intestinal brush border, SGLT1-dependent glucose uptake by K and L cells directly generates an electrical signal through the concomitant uptake of Na^+ ions, in turn triggering voltage-gated Ca^{2+} channel opening and Ca^{2+} -dependent hormone release (66). Rates of GLP-1 and GIP secretion by K and L cells thereby are linked to the rates of glucose absorption by neighboring enterocytes. Detection of ingested fat, by contrast, seems to largely depend on G-protein-coupled receptors (GPRs) that detect the triacylglycerol digestion products, fatty acids (sensed by GPR40 and GPR120), and monoacylglycerols (sensed by GPR119) (60). Of note, GPR40-dependent fatty acid detection by L cells also seems to depend on the rate of

nutrient absorption, as intestinal perfusion experiments have indicated that the receptor is accessible from the basolateral rather than luminal direction (67). Although close apposition of enteroendocrine cells with the terminals of enteric neurons has been described, the physiological role of neuronal signals in regulating gut hormone secretion remains uncertain (15). Expression of sweet taste receptors on gut endocrine cells, in particular L cells, has been reported as well as activation of these associated with increased secretion (68). Sweet taste receptor expression is not observed in mouse primary cells (69,70), however, and in humans, artificial sweeteners do not elicit incretin hormone secretion (71).

Some of most prominent metabolic effects of GLP-1 and GIP (in addition to the motility effects of GLP-1) are mediated through their direct actions on insulin-producing pancreatic β -cells. Receptors that detect GLP-1 (GLP1R) and GIP are highly expressed on the surface of β -cells, and binding of either hormone to its receptor triggers an intracellular signaling cascade resulting in elevated cytoplasmic concentrations of cAMP that in turn enhance rates of insulin release (72). A fundamental feature of GLP-1- and GIP-triggered insulin secretion is their glucose dependence: unless glucose concentrations are at or above normal levels, the cAMP signal in β -cells is largely ineffective. The translational importance of this finding is seen in people with type 2 diabetes treated with GLP-1 mimetics, which—unlike sulphonylureas or insulin—are not associated with an increase in the risk of hypoglycemia.

At the same time as they increase insulin secretion, GLP-1 and GIP modulate the release of the other pancreatic islet hormones glucagon and somatostatin. Whereas GIP enhances glucagon release (73), GLP-1 suppresses it. The suppression of glucagon secretion may contribute to the beneficial metabolic effect of GLP-1 because of the consequent reduction in hepatic glucose output (74). The mechanisms by which GLP-1 suppresses glucagon release remains a mystery because GLP1R is only detected on ~10% or less of glucagon-producing α -cells (75). An indirect pathway involving GLP1R-dependent stimulation of somatostatin secretion seems likely because somatostatin receptors generally are coupled to inhibition of their target cells. This concept is supported by

studies on perfused pancreas that showed a loss of GLP-1–inhibited glucagon release in the presence of somatostatin receptor inhibitors (76).

Exaggerated secretion of GLP-1 resulting in enhanced insulin secretion appears to be one of the important mechanisms underlying the resolution of diabetes often seen after gastric bypass surgery, as illustrated in experiments involving the GLP1R antagonist exendin 9-39, which eliminates the effect of the operation on insulin secretion and impairs glucose tolerance (77). The power of this mechanism is also illustrated by cases of reactive hypoglycemia after the operation, which may also be prevented by the antagonist (78), or by feeding through gastrostomy catheter, which eliminates the exaggerated GLP-1 response (79); the latter is in keeping with the principle that hypoglycemia results from extremely rapid carbohydrate entry into the small intestine (39).

Gut Microbiota and Glucose Handling

Alterations to the gut microbiota have been observed in numerous diseases, including human metabolic diseases such as obesity, type 2 diabetes, and irritable bowel syndrome, and some animal experiments have suggested causality (80). However, few studies have validated causality in humans, and the underlying mechanisms largely remain to be elucidated. In studies of the microbiome of patients randomly assigned to Roux-en-Y gastric bypass or vertical banded gastroplasty, similar and durable changes on the gut microbiome resulted in altered levels of fecal and circulating metabolites (81). In germ-free mice colonized with stools from the patients, reduced fat deposition was found. The results suggest that the gut microbiota play a direct role in the reduction of adiposity observed after bariatric surgery (81) and that the changes were mainly due to weight loss. On the other hand, elimination of colonic microbiota has little or no effect on glucose metabolism in humans (82,83).

CONCLUDING REMARKS

This review analyzed important factors of the gastrointestinal tract for glucose regulation in humans. Some are intrinsic to the gut and are essential parts of the absorptive process, including propulsive activity, increasing nutrient exposure to the mucosal surface, digestive and absorptive mechanisms, and intestinal

blood flow. The emptying of the stomach, in particular, perhaps represents the most powerful of all mechanisms regulating postprandial glucose concentrations. Gastrointestinal function in turn is regulated by metabolic, endocrine, and neuronal signals generated in the gut or associated with vagal activity; these signals influence the secretion of gut hormones that regulate appetite (and thereby food intake), gastrointestinal motility, and pancreatic endocrine functions. Among the gut hormones are the incretin hormones, which ensure that postprandial glucose excursions are kept low and relatively constant, despite variable amounts of ingested carbohydrates, through actions on insulin secretion and gut motility. We view the prandial regulation of hepatic glucose production as resulting mainly from the actions of portal glucose and the pancreatic islet hormones, although studies in experimental animals have suggested that central regulation may also play a role. New studies show that the intestinal microbiota may also influence metabolism (e.g., through production of short-chain fatty acids and bile acid metabolism).

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References

- Madsbad S, Kehlet H, Hilsted J, Tronier B. Discrepancy between plasma C-peptide and insulin response to oral and intravenous glucose. *Diabetes* 1983;32:436–438
- Perley MJ, Kipnis DM. Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic subjects. *J Clin Invest* 1967;46:1954–1962
- McIntyre N, Holdsworth CD, Turner DS. New interpretation of oral glucose tolerance. *Lancet* 1964;2:20–21
- Nauck MA, Homberger E, Siegel EG, et al. Incretin effects of increasing glucose loads in man calculated from venous insulin and C-peptide responses. *J Clin Endocrinol Metab* 1986;63:492–498
- Bagger JI, Knop FK, Lund A, Vestergaard H, Holst JJ, Vilsbøll T. Impaired regulation of the incretin effect in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2011;96:737–745
- Hare KJ, Vilsbøll T, Holst JJ, Knop FK. Inappropriate glucagon response after oral compared with isoglycemic intravenous glucose administration in patients with type 1 diabetes. *Am J Physiol Endocrinol Metab* 2010;298:E832–E837

- Lindgren O, Carr RD, Deacon CF, et al. Incretin hormone and insulin responses to oral versus intravenous lipid administration in humans. *J Clin Endocrinol Metab* 2011;96:2519–2524
- Holst JJ. On the physiology of GIP and GLP-1. *Horm Metab Res* 2004;36:747–754
- Nauck M, Stöckmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia* 1986;29:46–52
- Alfa RW, Park S, Skelly KR, et al. Suppression of insulin production and secretion by a incretin hormone. *Cell Metab* 2015;21:323–333
- Stenquist B, Knutson U, Olbe L. Gastric acid responses to adequate and modified sham feeding and to insulin hypoglycemia in duodenal ulcer patients. *Scand J Gastroenterol* 1978;13:357–362
- Schwartz TW, Stenquist B, Olbe L. Cephalic phase of pancreatic-polypeptide secretion studied by sham feeding in man. *Scand J Gastroenterol* 1979;14:313–320
- Veedefald S, Plamboeck A, Deacon CF, et al. Cephalic phase secretion of insulin and other enteropancreatic hormones in humans. *Am J Physiol Gastrointest Liver Physiol* 2016;310:G43–G51
- Holst JJ, Schwartz TW, Knuhtsen S, Jensen SL, Nielsen OV. Autonomic nervous control of the endocrine secretion from the isolated, perfused pig pancreas. *J Auton Nerv Syst* 1986;17:71–84
- Hansen L, Lampert S, Mineo H, Holst JJ. Neural regulation of glucagon-like peptide-1 secretion in pigs. *Am J Physiol Endocrinol Metab* 2004;287:E939–E947
- Horowitz M, Dent J, Fraser R, Sun W, Hebbard G. Role and integration of mechanisms controlling gastric emptying. *Dig Dis Sci* 1994;39(Suppl.):75–135
- Jones KL, O'Donovan D, Russo A, et al. Effects of drink volume and glucose load on gastric emptying and postprandial blood pressure in healthy older subjects. *Am J Physiol Gastrointest Liver Physiol* 2005;289:G240–G248
- Brener W, Hendrix TR, McHugh PR. Regulation of the gastric emptying of glucose. *Gastroenterology* 1983;85:76–82
- Horowitz M, Edelbroek MA, Wishart JM, Straathof JW. Relationship between oral glucose tolerance and gastric emptying in normal healthy subjects. *Diabetologia* 1993;36:857–862
- Jones KL, Horowitz M, Carney BI, Wishart JM, Guha S, Green L. Gastric emptying in early noninsulin-dependent diabetes mellitus. *J Nucl Med* 1996;37:1643–1648
- Jacobsen SH, Bojsen-Møller KN, Dirksen C, et al. Effects of gastric bypass surgery on glucose absorption and metabolism during a mixed meal in glucose-tolerant individuals. *Diabetologia* 2013;56:2250–2254
- Ma J, Pilichiewicz AN, Feinle-Bisset C, et al. Effects of variations in duodenal glucose load on glycaemic, insulin, and incretin responses in type 2 diabetes. *Diabet Med* 2012;29:604–608
- Lentle RG, Janssen PW. Manipulating digestion with foods designed to change the physical characteristics of digesta. *Crit Rev Food Sci Nutr* 2010;50:130–145
- Horowitz M, Jones K, Edelbroek MA, Smout AJ, Read NW. The effect of posture on gastric

- emptying and intragastric distribution of oil and aqueous meal components and appetite. *Gastroenterology* 1993;105:382–390
25. Bohl M, Bjørnshave A, Rasmussen KV, et al. Dairy proteins, dairy lipids, and postprandial lipemia in persons with abdominal obesity (DairyHealth): a 12-wk, randomized, parallel-controlled, double-blinded, diet intervention study. *Am J Clin Nutr* 2015;101:870–878
 26. Little TJ, Doran S, Meyer JH, et al. The release of GLP-1 and ghrelin, but not GIP and CCK, by glucose is dependent upon the length of small intestine exposed. *Am J Physiol Endocrinol Metab* 2006;291:E647–E655
 27. Allescher HD, Daniel EE, Dent J, Fox JE, Kostolanska F. Neural reflex of the canine pylorus to intraduodenal acid infusion. *Gastroenterology* 1989;96:18–28
 28. Levin F, Edholm T, Schmidt PT, et al. Ghrelin stimulates gastric emptying and hunger in normal-weight humans. *J Clin Endocrinol Metab* 2006;91:3296–3302
 29. Wettergren A, Schjoldager B, Mortensen PE, Myhre J, Christiansen J, Holst JJ. Truncated GLP-1 (proglucagon 78-107-amide) inhibits gastric and pancreatic functions in man. *Dig Dis Sci* 1993;38:665–673
 30. Gray GM, Ingelfinger FJ. Intestinal absorption of sucrose in man: interrelation of hydrolysis and monosaccharide product absorption. *J Clin Invest* 1966;45:388–398
 31. Wong JM, Jenkins DJ. Carbohydrate digestibility and metabolic effects. *J Nutr* 2007;137(Suppl.):2539S–2546S
 32. Puertollano E, Kolida S, Yaqoob P. Biological significance of short-chain fatty acid metabolism by the intestinal microbiome. *Curr Opin Clin Nutr Metab Care* 2014;17:139–144
 33. Troy S, Soty M, Ribeiro L, et al. Intestinal gluconeogenesis is a key factor for early metabolic changes after gastric bypass but not after gastric lap-band in mice. *Cell Metab* 2008;8:201–211
 34. Saeidi N, Meoli L, Nestoridi E, et al. Reprogramming of intestinal glucose metabolism and glycemic control in rats after gastric bypass. *Science* 2013;341:406–410
 35. Bantle AE, Wang Q, Bantle JP. Post-gastric bypass hyperinsulinemic hypoglycemia: fructose is a carbohydrate which can be safely consumed. *J Clin Endocrinol Metab* 2015;100:3097–3102
 36. Kellett GL. The facilitated component of intestinal glucose absorption. *J Physiol* 2001;531:585–595
 37. Thazhath SS, Marathe CS, Wu T, et al. The glucagon-like peptide 1 receptor agonist exenatide inhibits small intestinal motility, flow, transit, and absorption of glucose in healthy subjects and patients with type 2 diabetes: a randomized controlled trial. *Diabetes* 2016;65:269–275
 38. Rhee NA, Wahlgren CD, Pedersen J, et al. Effect of Roux-en-Y gastric bypass on the distribution and hormone expression of small-intestinal enteroendocrine cells in obese patients with type 2 diabetes. *Diabetologia* 2015;58:2254–2258
 39. Nguyen NQ, Debrenci TL, Bambrick JE, et al. Rapid gastric and intestinal transit is a major determinant of changes in blood glucose, intestinal hormones, glucose absorption and postprandial symptoms after gastric bypass. *Obesity (Silver Spring)* 2014;22:2003–2009
 40. Dirksen C, Jørgensen NB, Bojsen-Møller KN, et al. Gut hormones, early dumping and resting energy expenditure in patients with good and poor weight loss response after Roux-en-Y gastric bypass. *Int J Obes* 2013;37:1452–1459
 41. Berg P, McCallum R. Dumping syndrome: a review of the current concepts of pathophysiology, diagnosis, and treatment. *Dig Dis Sci* 2016;61:11–18
 42. Trahair LG, Horowitz M, Hausken T, Feinle-Bisset C, Rayner CK, Jones KL. Effects of exogenous glucagon-like peptide-1 on the blood pressure, heart rate, mesenteric blood flow, and glycemic responses to intraduodenal glucose in healthy older subjects. *J Clin Endocrinol Metab* 2014;99:E2628–E2634
 43. Goldfine AB, Mun EC, Devine E, et al. Patients with neuroglycopenia after gastric bypass surgery have exaggerated incretin and insulin secretory responses to a mixed meal. *J Clin Endocrinol Metab* 2007;92:4678–4685
 44. Ramnanan CJ, Edgerton DS, Cherrington AD. Evidence against a physiologic role for acute changes in CNS insulin action in the rapid regulation of hepatic glucose production. *Cell Metab* 2012;15:656–664
 45. Schwartz MW, Seeley RJ, Tschöp MH, et al. Cooperation between brain and islet in glucose homeostasis and diabetes. *Nature* 2013;503:59–66
 46. Patti ME, McMahon G, Mun EC, et al. Severe hypoglycemia post-gastric bypass requiring partial pancreatectomy: evidence for inappropriate insulin secretion and pancreatic islet hyperplasia. *Diabetologia* 2005;48:2236–2240
 47. Jørgensen NB, Jacobsen SH, Dirksen C, et al. Acute and long-term effects of Roux-en-Y gastric bypass on glucose metabolism in subjects with type 2 diabetes and normal glucose tolerance. *Am J Physiol Endocrinol Metab* 2012;303:E122–E131
 48. Nijima A. Neural mechanisms in the control of blood glucose concentration. *J Nutr* 1989;119:833–840
 49. Hölzer HH, Turkelson CM, Solomon TE, Raybould HE. Intestinal lipid inhibits gastric emptying via CCK and a vagal capsaicin-sensitive afferent pathway in rats. *Am J Physiol* 1994;267:G625–G629
 50. Kronborg O. Clinical results 6 to 8 years after truncal vagotomy and drainage for duodenal ulcer in 500 patients. *Acta Chir Scand* 1975;141:657–663
 51. Plamboeck A, Veefald S, Deacon CF, et al. Characterisation of oral and i.v. glucose handling in truncally vagotomised subjects with pyloroplasty. *Eur J Endocrinol* 2013;169:187–201
 52. Seoane-Collazo P, Fernø J, Gonzalez F, et al. Hypothalamic-autonomic control of energy homeostasis. *Endocrine* 2015;50:276–291
 53. Duca FA, Bauer PV, Hamr SC, Lam TK. Glucoregulatory relevance of small intestinal nutrient sensing in physiology, bariatric surgery, and pharmacology. *Cell Metab* 2015;22:367–380
 54. Rasmussen BA, Breen DM, Luo P, et al. Duodenal activation of cAMP-dependent protein kinase induces vagal afferent firing and lowers glucose production in rats. *Gastroenterology* 2012;142:834–843
 55. Rasmussen BA, Breen DM, Duca FA, et al. Jejunal leptin-PI3K signaling lowers glucose production. *Cell Metab* 2014;19:155–161
 56. Baum F, Nauck MA, Ebert R, et al. Role of endogenously released cholecystokinin in determining postprandial insulin levels in man: effects of loxiglumide, a specific cholecystokinin receptor antagonist. *Digestion* 1992;53:189–199
 57. Cummings DE, Overduin J. Gastrointestinal regulation of food intake. *J Clin Invest* 2007;117:13–23
 58. Grill HJ, Hayes MR. Hindbrain neurons as an essential hub in the neuroanatomically distributed control of energy balance. *Cell Metab* 2012;16:296–309
 59. Sjölund K, Sandén G, Håkanson R, Sundler F. Endocrine cells in human intestine: an immunocytochemical study. *Gastroenterology* 1983;85:1120–1130
 60. Gribble FM, Reimann F. Enteroendocrine cells: chemosensors in the intestinal epithelium. *Annu Rev Physiol* 2016;78:277–299
 61. Miholic J, Orskov C, Holst JJ, Kotzerke J, Meyer HJ. Emptying of the gastric substitute, glucagon-like peptide-1 (GLP-1), and reactive hypoglycemia after total gastrectomy. *Dig Dis Sci* 1991;36:1361–1370
 62. Schirra J, Katschinski M, Weidmann C, et al. Gastric emptying and release of incretin hormones after glucose ingestion in humans. *J Clin Invest* 1996;97:92–103
 63. Færch K, Torekov SS, Vistisen D, et al. GLP-1 response to oral glucose is reduced in prediabetes, screen-detected type 2 diabetes, and obesity and influenced by sex: the ADDITION-PRO study. *Diabetes* 2015;64:2513–2525
 64. Nauck MA, Vardarli I, Deacon CF, Holst JJ, Meier JJ. Secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down? *Diabetologia* 2011;54:10–18
 65. Nguyen NQ, Debrenci TL, Bambrick JE, et al. Accelerated intestinal glucose absorption in morbidly obese humans: relationship to glucose transporters, incretin hormones, and glycemia. *J Clin Endocrinol Metab* 2015;100:968–976
 66. Gribble FM, Williams L, Simpson AK, Reimann F. A novel glucose-sensing mechanism contributing to glucagon-like peptide-1 secretion from the GLUTag cell line. *Diabetes* 2003;52:1147–1154
 67. Christensen LW, Kuhre RE, Janus C, Svendsen B, Holst JJ. Vascular, but not luminal, activation of FFAR1 (GPR40) stimulates GLP-1 secretion from isolated perfused rat small intestine. *Physiol Rep* 2015;3:3
 68. Jang HJ, Kokrashvili Z, Theodorakis MJ, et al. Gut-expressed gustducin and taste receptors regulate secretion of glucagon-like peptide-1. *Proc Natl Acad Sci U S A* 2007;104:15069–15074
 69. Parker HE, Habib AM, Rogers GJ, Gribble FM, Reimann F. Nutrient-dependent secretion of glucose-dependent insulinotropic polypeptide from primary murine K cells. *Diabetologia* 2009;52:289–298
 70. Tolhurst G, Reimann F, Gribble FM. Nutritional regulation of glucagon-like peptide-1 secretion. *J Physiol* 2009;587:27–32
 71. Maersk M, Belza A, Holst JJ, et al. Satiety scores and satiety hormone response after

- sucrose-sweetened soft drink compared with isocaloric semi-skimmed milk and with non-caloric soft drink: a controlled trial. *Eur J Clin Nutr* 2012;66:523–529
72. Drucker DJ. The biology of incretin hormones. *Cell Metab* 2006;3:153–165
73. Lund A, Vilsbøll T, Bagger JI, Holst JJ, Knop FK. The separate and combined impact of the intestinal hormones, GIP, GLP-1, and GLP-2, on glucagon secretion in type 2 diabetes. *Am J Physiol Endocrinol Metab* 2011;300:E1038–E1046
74. Hvidberg A, Nielsen MT, Hilsted J, Orskov C, Holst JJ. Effect of glucagon-like peptide-1 (proglucagon 78-107amide) on hepatic glucose production in healthy man. *Metabolism* 1994;43:104–108
75. Richards P, Parker HE, Adriaenssens AE, et al. Identification and characterization of GLP-1 receptor-expressing cells using a new transgenic mouse model. *Diabetes* 2014;63:1224–1233
76. de Heer J, Rasmussen C, Coy DH, Holst JJ. Glucagon-like peptide-1, but not glucose-dependent insulintropic peptide, inhibits glucagon secretion via somatostatin (receptor subtype 2) in the perfused rat pancreas. *Diabetologia* 2008;51:2263–2270
77. Jørgensen NB, Dirksen C, Bojsen-Møller KN, et al. Exaggerated glucagon-like peptide 1 response is important for improved β -cell function and glucose tolerance after Roux-en-Y gastric bypass in patients with type 2 diabetes. *Diabetes* 2013;62:3044–3052
78. Salehi M, Gastaldelli A, D'Alessio DA. Blockade of glucagon-like peptide 1 receptor corrects postprandial hypoglycemia after gastric bypass. *Gastroenterology* 2014;146:669–680
79. McLaughlin T, Peck M, Holst J, Deacon C. Reversible hyperinsulinemic hypoglycemia after gastric bypass: a consequence of altered nutrient delivery. *J Clin Endocrinol Metab* 2010;95:1851–1855
80. Wu H, Tremaroli V, Bäckhed F. Linking microbiota to human diseases: a systems biology perspective. *Trends Endocrinol Metab* 2015;26:758–770
81. Tremaroli V, Karlsson F, Werling M, et al. Roux-en-Y gastric bypass and vertical banded gastroplasty induce long-term changes on the human gut microbiome contributing to fat mass regulation. *Cell Metab* 2015;22:228–238
82. Mikkelsen KH, Frost M, Bahl MI, et al. Effect of antibiotics on gut microbiota, gut hormones and glucose metabolism. *PLoS One* 2015;10:e0142352
83. Vrieze A, Out C, Fuentes S, et al. Impact of oral vancomycin on gut microbiota, bile acid metabolism, and insulin sensitivity. *J Hepatol* 2014;60:824–831