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Glucoregulatory Relevance of Small Intestinal Nutrient Sensing in Physiology, Bariatric Surgery, and Pharmacology

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Emerging evidence suggests the gastrointestinal tract plays an important glucoregulatory role. In this perspective, we first review how the intestine senses ingested nutrients, initiating crucial negative feedback mechanisms through a gut-brain neuronal axis to regulate glycemia, mainly via reduction in hepatic glucose production. We then highlight how intestinal energy sensory mechanisms are responsible for the glucose-lowering effects of bariatric surgery, specifically duodenal-jejunal bypass, and the antidiabetic agents metformin and resveratrol. A better understanding of these pathways lays the groundwork for intestinally targeted drug therapy for the treatment of diabetes.

Introduction

For the first time in the modern era, life expectancy of the current generation is predicted to be lower than that of its predecessor, due in large part to the rapidly rising rates of obesity over the past half century. An overwhelming obesogenic environment, the backdrop to a globally expanding western lifestyle, has led to a ''diabesity'' pandemic that represents a costly and urgent global health crisis. Despite much medical and technological advancement, not only does the pathogenesis of obesity and diabetes remain poorly understood, but also modern society is in a unique position where current treatments are being utilized despite not having a clear grasp of the mechanisms of action. For example, gastric bypass surgery is currently one of the most successful options for reduction of body weight and improvements in glucose homeostasis, despite the mechanisms involved remaining relatively unknown. The success of gastric bypass surgery, given it involves a rearrangement of the intestinal tract, and several new promising gut-derived diabetes and obesity treatments, such as GLP-1 analogs, highlight the role of the gastrointestinal (GI) tract in metabolic diseases. Indeed, the traditional view of the GI tract as mainly having a macro- and micro-nutrient absorptive function has shifted to it being an important player in many physiological systems, from immunity to metabolic homeostasis.

The gut is a mediator between ingested nutrients and the body, providing crucial information about the size and composition of a meal and initiating negative feedback pathways via a gut-brain axis to control food intake (Cummings and Overduin, 2007). The metabolic role of the GI tract is recently extended, as gut-derived signaling pathways induce thermogenesis, increase energy expenditure, alter central food reward signaling, promote insulin secretion, and lower hepatic glucose production (HGP) (Baggio et al., 2004; Blouet and Schwartz, 2012; Scrocchi et al., 1996; Tellez et al., 2013; Wang et al., 2008). Although the relative clinical metabolic contribution of the gut-brain axis compared to the traditional view that glucose homeostasis is mediated via peripheral endocrine regulation (pancreatic insulin and glucagon) remains to be thoroughly tested, the understanding of these gut-derived pathways will lay the groundwork for gut-targeted therapeutics for diabetes and obesity. In this perspective, we highlight how intestinal nutrient sensing regulates glucose homeostasis in a normal physiological setting as well as mediates the beneficial glucose-lowering effects of surgical and pharmacological therapies.

Intestinal Nutrient Sensing

Preabsorptive nutrients trigger complex and integrative gut-brain negative feedback axes to prevent energy excess by suppressing food intake and endogenous nutrient production. Intestinal nutrients signal mainly through the release of GI peptides, which act on central targets in an endocrine fashion, or through local, paracrine action on nerve terminals innervating the gut. Alternatively, nutrients themselves act alone, or in cohort with gut peptides, to activate afferent neurons (Burcelin et al., 2001; Darling et al., 2014) (Figure 1). Gut peptides are synthesized in enteroendocrine cells (EECs) of the gut epithelial mucosa. The EECs are exposed to the intestinal lumen on their apical sides and secrete peptides from their basolateral sides and are in close proximity to nerve endings expressing gut peptide receptors, supporting local, paracrine signaling (Richards et al., 2014). Classically, EECs are characterized by the peptides that they produce. The proximal small intestine contains I cells and K cells, which produce cholecystokinin (CCK) and glucose-dependent insulinotropic hormone (GIP), respectively, while the distal small intestine and colon contain L cells, which produce glucagon-like peptide-1/2 (GLP-1/2), oxyntomodulin and peptide YY (PYY). However, recent findings indicate strong co-expression of these peptides within various EECs throughout the small intestine, refuting the accepted classification system and suggesting that EECs may in fact be

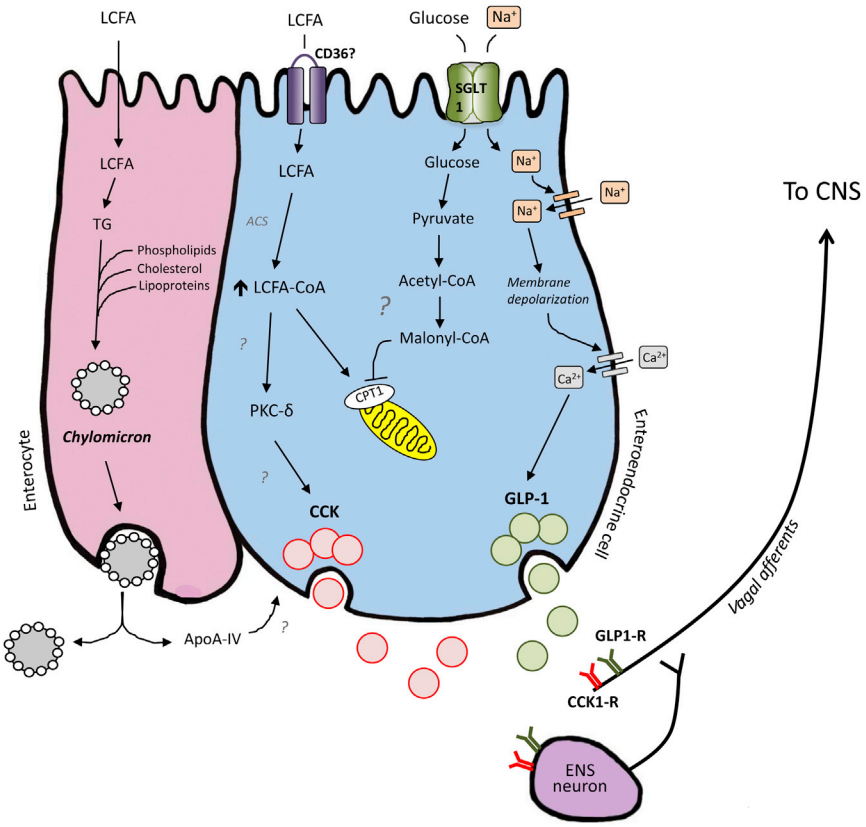

Figure 1. Lipid- and Glucose-Sensing Mechanisms in the Duodenum

In EECs, uptake of lipids, possibly via CD36, leads to an accumulation of LCFA-CoA, which stimulates CCK release via PKC-δ. SGLT1 expressed on EECs mediates glucose uptake, and upon activation by glucose, this transporter causes membrane depolarization, calcium influx, and gut peptide release. Alternatively, we hypothesize that intracellular metabolism of glucose to malonyl-coA inhibits CPT-1-mediated uptake of LCFA-CoA into mitochondria, which stimulates gut peptide release in a similar fashion to that of lipid-induced release of CCK by increasing cytosolic LCFA-CoA levels. As opposed to direct EEC activation, ingested lipids passively diffuse into enterocytes and are metabolized into chylomicrons. After secretion, chylomicron-associated signaling molecules, such as Apo-AIV, stimulate gut peptide secretion from adjacent EECs through unknown mechanisms. ApoA-IV, Apolipoprotein A-IV; Ca^{2+}, calcium ion; CCK, cholecystokinin; CCK1-R, cholecystokinin receptor 1; CD36, cluster of differentiation 36; CNS, central nervous system; CPT1, carnitine palmitoyltransferase 1; ENS; enteric nervous system; GLP-1, glucagon like peptide 1; GLP1-R, glucagon-like peptide 1 receptor; PKC-δ, protein kinase C-δ; LCFA, long-chain fatty acid; Na^+, sodium ion; SGLT1, sodium-dependent glucose co-transporter; TG, triglyceride.

represented by a single cell type with varying expression of the different peptides (Habib et al., 2012). Nonetheless, EECs are activated by a variety of nutrient-dependent machineries that trigger membrane depolarization, second messenger cascades, and intracellular calcium elevation to stimulate gut peptide release (Psichas et al., 2015) (Figure 1).

G protein-coupled receptors (GPCRs) such as fatty-acid-specific GPR40 and protein-sensitive CaSR colocalize with gut peptides (Edfalk et al., 2008; Hirasawa et al., 2005; Liou et al., 2011), as do electrogenic solute transporters such as sodium-coupled glucose transporter 1 (SGLT-1) that trigger membrane depolarization and calcium entry independent of intracellular nutrient metabolism (Reimann et al., 2008). Nutrient uptake and metabolism alternatively activate signaling pathways involving long-chain fatty acid-CoA (LCFA-CoA) that trigger CCK-mediated signaling pathways (Wang et al., 2008). Lipid absorption by enterocytes and the subsequent packaging into chylomicrons may be necessary for ingested lipids to stimulate CCK and GIP release as well (Lo et al., 2007; Lu et al., 2012; Raybould et al., 1998; Whited et al., 2005), while the release of ApoA-IV may also be involved (Lo et al., 2007; Whited et al., 2005). Once the gut peptides are secreted, they either enter the circulation to act on central and peripheral targets or communicate with the brain indirectly by acting locally on afferent nerve terminals. In fact, both spinal and vagal afferents innervate the lamina propria of the gut wall with their terminals in close proximity of EECs. While spinal afferents are implicated (Raybould and Hölzer, 1992), most studies demonstrate vagal afferent nerve terminals mediate the gut-brain negative feedback relays given that vagal afferents express CCK, GLP-1, PYY, and leptin receptors (Dockray, 2013).

Gut peptides also activate vagal afferents indirectly, as neurons of the enteric nervous system (ENS) relay nutrient-derived signals to the CNS (Ritter, 2011) and respond to GLP-1 and CCK (Amato et al., 2010; Patterson et al., 2002; Richards et al., 2014), although the ENS is classically known to control intestinal function (Costa et al., 2000). One study even suggests that fatty acids act directly on GPR40 expressed on vagal afferents to suppress food intake (Darling et al., 2014), bypassing gut peptide secretion and adding to the complexity of intestinal nutrient sensing. Nevertheless, activation of this vagal gut-brain axis is vital for nutrient-triggered negative feedback, since treating the gut with anesthetics, neurotoxins, or vagotomy abolishes the effects of intestinal nutrients on food intake and glucose regulation (Schwartz, 2011). Vagal afferent fibers terminate in the nucleus tractus solitarius (NTS) of the hindbrain, and antagonism of N-methyl-D-aspartate (NMDA) receptors in the NTS reverses the effects of intestinal nutrients or CCK to lower food intake or suppress HGP (Cheung et al., 2009; Wang et al., 2008; Wright et al., 2011). Intestinal CCK-mediated activation of NTS NMDA receptors leads to MAPK-ERK1/2 signaling and phosphorylation of synapsin I in hindbrain neurons (Campos et al., 2012), and through unclear mechanisms, these neurons act as a relay for vagal gut-derived signals to control food intake or suppress HGP via the hepatic vagal efferent (Wang et al., 2008).

While the role of nutrient-induced feedback in the control of food intake is extensively studied and reviewed elsewhere (Cummings and Overduin, 2007), more recent work has established a glucoregulatory role of intestinal nutrient sensing. Given that the majority of nutrients are absorbed in the duodenum, the small

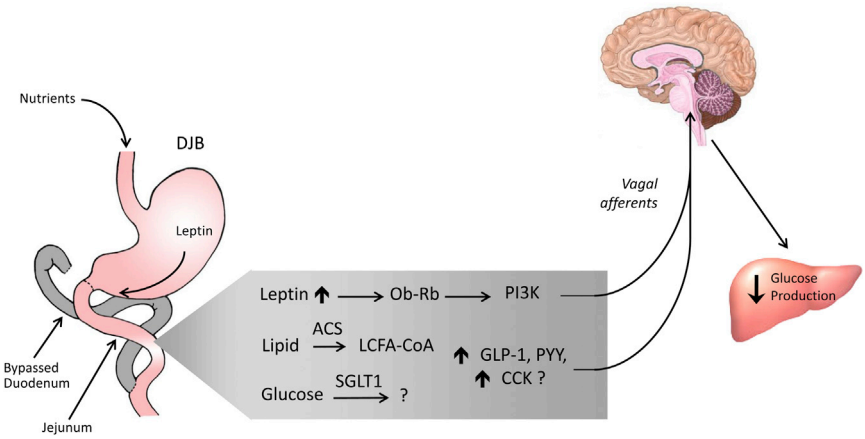

Figure 2. Jejunal-Sensing Mechanisms following DJB Surgery

Increased nutrient influx results in the activation of nutrient-sensing pathways in the jejunum that trigger gut peptide release and the activation of a gut-brain-liver axis to lower glucose production. Exclusion of the duodenum results in increased influx of gastric leptin into the distal small intestine, which activates signaling pathways that ultimately trigger vagal afferent firing to lower HGP. DJB, duodenal-jejunal bypass; Ob-Rb, functional long form leptin receptor; PI3K, phosphoinositide-3-kinase; ACS, acetyl CoA synthetase; LCFA-CoA, long-chain fatty acid-CoA; SGLT1, sodium glucose transporter 1; GLP-1, glucagon-like peptide 1; PYY, peptide YY; CCK, cholecystokinin.

intestine likely represents the major site of direct intestinal nutrient sensing, consistent with possessing the highest level of vagal innervation throughout the intestines (Berthoud et al., 1995). While jejunal nutrient-sensing mechanisms exist (Figure 2) and act through conserved mechanisms to those present in the duodenum, it is apparent that more distal nutrient sensing only becomes relevant in the context of surgical rearrangement of the gut (see Bariatric Surgery), while duodenal nutrient-sensing mechanisms are necessary for normal glucose homeostasis during physiological re-feeding conditions (Breen et al., 2012; Cheung et al., 2009; Kokorovic et al., 2011).

Duodenal Gut-Brain Axis

Acute intraduodenal infusion of a lipid emulsion lowers HGP through a gut-brain-liver neuronal axis in healthy rodents, which is dependent upon intestinal CCK-1 signaling (Cheung et al., 2009; Wang et al., 2008). This glucose-lowering effect requires uptake of LCFA and subsequent intracellular esterification to LCFA-CoA by acyl-CoA synthetase (ACS) (Wang et al., 2008). While the involvement of fatty acid transporters in the glucoregulatory effects of intraduodenal lipids has not been tested, a likely role of fatty acid transporter cluster of differentiation 36 (CD36) is presented given that *CD36*$^{-/-}$ mice exhibit a reduced satiety response as well as reduced CCK release in response to intestinal lipids (Schwartz et al., 2008; Sundaresan et al., 2013) (Figure 1). Furthermore, the glucose-lowering effect of LCFAs is mediated by the activation of duodenal protein kinase C (PKC)-δ, which is expressed in rodent and human duodenal mucosa (Breen et al., 2011; Kokorovic et al., 2011), consistent with studies reporting that PKC-δ mediates LCFA-induced CCK secretion from STC-1 cells (Chang et al., 2000; Takahashi et al., 2000). Although the downstream signaling events of PKC-δ remain unclear, this glucose-lowering LCFA→LCFA-CoA→PKC-δ axis requires activation of duodenal CCK-1 receptors (CCK-1R) (Breen et al., 2011; Cheung et al., 2009).

The CCK-1R is a GPCR, possessing domains for G_s and G_q (Cawston and Miller, 2010). Although studies highlight that CCK-1R activation induces G_q-dependent pathways in various cell types (Cawston and Miller, 2010; Matozaki and Williams, 1989), CCK-1R activation increases cyclic AMP levels as well (Wu et al., 1997), while both phospholipase C and protein kinase A (PKA) are necessary for CCK to activate central vagal afferent terminals (Rogers and Hermann, 2008). Similarly, intestinal CCK-1R signaling via PKA mediates intestinal CCK to increase vagal afferent firing and lower HGP (Rasmussen et al., 2012), consistent with the fact that CCK-1R is localized on vagal afferent terminals that innervate the duodenal mucosa (Raybould et al., 1988). Further, activation of the duodenal lipid-PKA pathway triggers NMDA receptor transmission in the NTS to lower HGP via the hepatic vagal branch (Rasmussen et al., 2012). These results indicate that duodenal lipid sensing regulates HGP via a local LCFA→LCFA-CoA→PKC-δ→CCK→CCK1R→PKA signaling axis, which activates a gut-brain-liver neuronal axis to lower HGP in healthy rodents (Côté et al., 2014).

Interestingly, the necessity for LCFA-CoA accumulation and activation of PKC-δ in the gut to lower HGP mirrors the glucose-lowering effect of mediobasal hypothalamus nutrient sensing (Duca and Yue, 2014). Carnitine palmitoyltransferase-1 (CPT-1) regulates the transport of LCFA-CoA into the mitochondria for β-oxidation, such that inhibiting hypothalamic CPT-1 elevates cytoplasmic LCFA-CoA levels, thereby triggering a brain-liver axis that inhibits HGP (Obici et al., 2003). It is therefore likely that inhibiting CPT-1 in the gut increases intestinal LCFA-CoA levels and thus triggers the aforementioned gut-brain-liver axis to lower HGP (Figure 1); however, this remains to be investigated.

In the brain, malonyl-CoA inhibits CPT-1 activity and elevates hypothalamic LCFA-CoA to lower HGP (Caspi et al., 2007; He et al., 2006). The ability of glucose in the hypothalamus to suppress HGP is reversed when the conversion of acetyl-CoA to malonyl-CoA is inhibited via activation of AMP-dependent protein kinase (AMPK) (Yang et al., 2010). Thus, malonyl-CoA is a converging molecule through which lipid and glucose sensing in the brain lowers HGP. Although the role of duodenal glucose-sensing in the regulation of HGP has not been investigated, a likely model exists where intestinal glucose is metabolized to malonyl-CoA, contributing to the accumulation of LCFA-CoA and triggering a PKC-δ→CCK-mediated gut-brain axis to lower HGP (Figure 1). However, it is to be noted that glucose is more recognized to release GLP-1 instead of CCK (Richards et al., 2014).

The idea that intracellular metabolism of glucose leads to gut peptide release implicates a role of SGLT-1, which is responsible for glucose uptake in the intestinal epithelium (Dobbins et al., 2015). In fact, generation of *SGLT1*$^{-/-}$ mice reveals not only

impaired glucose absorption but also impaired glucose-induced release of GLP-1 (Gorboulev et al., 2012). Interestingly, recent studies report non-metabolizable substrates of SGLT-1 stimulate GLP-1 release (Moriya et al., 2009; Reimann et al., 2008), suggesting that activation of SGLT-1 per se leads to GLP-1 release independent of glucose cellular metabolism (Figure 1). Further, GLUT activity, but not SGLT-1, mediates intracellular glucose concentrations, while the electrogenic property of SGLT-1 activation is sufficient to cause membrane depolarization and Ca^{2+} entry in L cells (Parker et al., 2012). Future studies are clearly required to dissect the mechanisms of preabsorptive glucose sensing in the intestine with regards to intracellular glucose metabolism versus cell surface SGLT1 activation in vivo.

Given the short half-life of GLP-1 in circulation (Holst, 2007) and GLP-1 receptors (GLP-1Rs) are expressed in the nodose ganglia that contain the cell bodies for vagal afferents innervating the intestine and hepatoportal vein (Nakagawa et al., 2004), it is likely that GLP-1 acts in the gut or portal region to stimulate a gut-brain metabolic axis (Hayes et al., 2010). GLP-1Rs in the hepatoportal vein are necessary for portal glucose and GLP-1 signaling to regulate glucose tolerance (Burcelin et al., 2001; Vahl et al., 2007), while portal infusion of GLP-1 induces a vagal hepatopancreatic reflex as well (Nakabayashi et al., 1996). The expression of GLP-1R protein in the portal vein has been documented, but the specificity of the antibody was not properly established (Vahl et al., 2007; Panjwani et al., 2013), thus questioning whether GLP-1R in the nodose ganglia is actually transported to the afferent terminals innervating the portal vein (and possibly GI tract). On the other hand, GLP-1R expression in vagal afferents is, after all, possible given that the receptor for another L-cell-derived peptide, PYY, is synthesized in the nodose ganglia and axonally transported (Koda et al., 2005). In addition, GLP-1R-positive neurons are in close proximity to intestinal GLP-1-secreting cells (although it was not determined if these were vagal afferent or non-vagal) (Richards et al., 2014). Future studies are warranted to further characterize the vagal distribution of GLP-1R expression.

Physiological Role of Intestinal Nutrient Sensing

It is important to reiterate again that intestinal nutrient-sensing mechanisms exhibit a physiological glucoregulatory role. For example, in line with the fact that the anorectic effect of ingested nutrients is abolished with the administration of a CCK-1R antagonist in rats (Bellissimo and Anderson, 2003) and humans (Beglinger et al., 2001), normal glucose homeostasis is disrupted with intraduodenal CCK-1R antagonist infusion or in Otsuka Long-Evans Tokushima fatty (OLEFT) rats (which lack the CCK-1R) during a fasting-refeeding protocol independent of changes in food intake (Cheung et al., 2009). Inhibition of duodenal PKC-δ, which lies upstream of CCK-1R signaling in lipid-induced lowering of HGP, similarly impairs regulation of plasma glucose levels during the same fasting-refeeding paradigm (Breen et al., 2011; Kokorovic et al., 2011). These observations are strengthened by the fact that OLETF rats are hyperglycemic and hyperinsulinemic (Kawano et al., 1992), although both the impairment of CCK-1R signaling and the genetic susceptibility of the Long-Evans strain (Yamada et al., 2012) may contribute to these metabolic disturbances, as *CCK-1R* knockout (KO) F344 rats and mice are normoglycemic (Bi et al., 2007; Blevins et al., 2009). The clinical glucoregulatory role of CCK signaling remains to be assessed, but such a role has been implicated in the glucose-lowering effect of bile acid sequestrant treatment in people with impaired fasting glucose (Marina et al., 2012).

Similarly, portal infusion of exendin-9 impairs glucose tolerance in a pseudo-fasting-refeeding paradigm where fasted rats are anaesthetized and given a gastric bolus of glucose (Vahl et al., 2007). While exendin-9 increases blood glucose levels compared to saline injection following an OGTT in rats with vagal common hepatic branch ablation (eliminates vagal afferents of a hepatoportal origin), rats with a subdiaphragmatic vagotomy (eliminates all vagal afferents innervating the peritoneal cavity) do not respond to exendin-9 following OGTT (Hayes et al., 2011), suggesting that while vagal afferent fibers of the hepatoportal region may contribute to glycemic control, it is the vagal afferents innervating the intestine that are required for the physiological glucoregulatory effect of endogenous GLP-1 action. Whether GLP-1 activates vagal afferents innervating the intestine or portal vein in humans remains unknown. However, there is evidence that vagal GLP-1 signaling may play a role in glucose metabolism in humans.

Vagotomy in patients with duodenal ulcers impairs glucose tolerance following an oral, but not intravenous, glucose tolerance test (Humphrey et al., 1975). Two follow-up studies in patients with truncal vagotomy and pyloroplasty indicate that this effect may be due to GLP-1 vagal signaling, as these patients exhibit impaired GI -mediated glucose disposal following an OGTT in the face of increased GLP-1 levels (hypothesized to be due to the pyloroplasty), and these individuals have reduced insulinotropic and glucagonostatic effects following exogenous GLP-1 administration (Plamboeck et al., 2013a, 2013b). These studies suggest that vagal GLP-1 action improves oral glucose tolerance via a gut-brain-mediated secretion of insulin and/or glucagon, while GLP-1 could also directly lower HGP in humans during the pancreatic clamp (Seghieri et al., 2013), possibly via a gut-brain-liver axis. Not all studies in humans demonstrate a role for the vagus in glucose homeostasis (Corssmit et al., 1995), and although non-vagal neural signaling (spinal afferents) may mediate intestinal sensing mechanisms in humans, this is yet to be tested, together with the fact that only a few studies demonstrate a nutrient-sensing role of the spinal afferents in rodents (Raybould and Hölzer, 1992). Lastly, it is to be acknowledged that direct activation of the GLP-1R expressed in the pancreas (Campbell and Drucker, 2013) may also underlie the ability of exendin-9 to disrupt glucose tolerance in rodents (Kolligs et al., 1995; Wang et al., 1995) and humans (Edwards et al., 1999; Salehi et al., 2008) following an OGTT or a meal.

In summary, small intestinal nutrient-sensing mechanisms trigger hormonal pathways to control metabolic homeostasis. We next address whether these respective mechanisms could contribute to the metabolic benefits of bariatric surgery.

Bariatric Surgery

Bariatric surgery is currently the most successful treatment for sustained body weight reduction in obese individuals. The most effective and widely performed surgical technique is the Roux-en-Y gastric bypass (RYGB), which involves the formation of a small upper gastric pouch to which a roux jejunal limb is anastomosed. This procedure creates alimentary, biliopancreatic, and common limbs, thus excluding most of the stomach

and proximal intestine, thereby creating both restrictive and malabsportive components. RYGB provides significant and sustained weight loss, with up to 30% weight loss maintained for over 10 years (Karlsson et al., 2007); however, the benefits of RYGB extend well beyond weight loss and include metabolic benefits (Sjöström et al., 1999). In the case of diabetes remission, the effects on glucose control appear independent of weight loss, as dramatic improvements in these parameters occur rapidly, usually within 1 week, before any significant weight loss has been achieved (Schauer et al., 2003). Consequently, bariatric surgery is now being referred to as a "metabolic surgery" (Rubino, 2013) and is currently being explored as a treatment for type 2 diabetes (T2D) with some indication that surgical treatment results in greater glucose control than conventional medical therapy (Ikramuddin et al., 2013; Mingrone et al., 2012; Schauer et al., 2012). Although RYGB improvements were originally hypothesized to be due to its restrictive and malabsorptive capacity, a large body of evidence argues against this (Miras and le Roux, 2013; Stefater et al., 2010; Thaler and Cummings, 2009) and suggests that the main beneficial effects of RYGB are due to alterations in GI biology (Manning et al., 2015). Given the gross anatomical rearrangement of the GI tract, it is a safe assumption that the intestine exhibits vast and rapid metabolic adaptations that coincide with the early success of bariatric surgery.

To better tease out these intestinal adaptive mechanisms underlying the efficiency of RYGB, duodenal-jejunal bypass (DJB) surgery was developed, an experimental procedure that mimics the intestinal alterations present in RYGB by surgically excluding the duodenum and proximal jejunum while preserving the stomach (Wittgrove et al., 1996). Although DJB does not elicit the same weight loss effects as RYGB, it has similar gluco-regulatory effects (Hu et al., 2014; Jiao et al., 2013; Rubino et al., 2006; Salinari et al., 2014). Non-obese diabetic DJB rats show improved glucose homeostasis, independent of changes in food intake or body weight, as early as 1 week after the procedure and persisting for 9 months (Rubino and Marescaux, 2004; Speck et al., 2011). DJB also lowers glucose in non-obese (Cohen et al., 2012a; Cohen et al., 2007) or mild-obese (Lee et al., 2010) humans with T2D. Given that the rearrangement of the GI tract is the same for DJB and RYGB, improvements in glycemia following small bowel manipulations are hypothesized to be due to either a foregut or hindgut hypothesis. The foregut hypothesis suggests that excluding the proximal intestine diminishes a pathophysiological rise in an unknown "anti-incretin" signal that normally serves to counteract incretin-mediated insulin secretion and prevent hypoglycemia (Salinari et al., 2014). On the other hand, the hindgut hypothesis proposes glycemia improvements are due to alterations in the chemosensory capacity of the distal small intestine now exposed to an increased flux of unabsorbed nutrients and the subsequent release of gut peptides and communication to important metabolic organs. Indeed, gut hormone signaling has been extensively investigated in mediating the beneficial effects of bariatric surgery (Scott and Batterham, 2011), given that RYGB increases the number of gut-peptide-expressing EECs (Mumphrey et al., 2013) and, as such, postprandial gut peptide secretion (Madsbad et al., 2014).

One such candidate is GLP-1, as the increase in circulating GLP-1 levels following both RYGB (Chambers et al., 2011; Jiménez et al., 2013; Rodieux et al., 2008; Salehi et al., 2011) and DJB (Imoto et al., 2014; Kindel et al., 2009) have led many investigators to examine the role of GLP-1 signaling in the post-surgical effects of RYGB and DJB procedures. Exaggerated postprandial GLP-1 profiles occur as early as 2 days post-surgery (le Roux et al., 2007), persist as long as 10 years post-surgery (Dar et al., 2012), and are elicited by previously established subthreshold caloric loads (i.e., before surgery, meal size provides minimal stimulation of GLP-1 secretion, but after surgery, same meal size induces a significant rise in postprandial GLP-1) (Yan et al., 2014). Improvements in glucose tolerance following RYGB correlates with sensitivity to GLP-1 signaling, as only rats that respond to administration of exendin-4, a GLP-1R agonist, before surgery exhibit improved glucose tolerance following RYGB despite similar post-surgical body weight loss among responders and non-responders (Habegger et al., 2014b). In humans, poor weight loss in patients that received gastric bypass is associated with attenuated postprandial GLP-1 response, although changes in glycemic control were not measured (Dirksen et al., 2013; le Roux et al., 2007), while improvements in glucose tolerance following RYGB (Chambers et al., 2011) and DJB (Imoto et al., 2014; Kindel et al., 2009) are abolished with exendin-9 administration. However, the involvement of GLP-1 in the beneficial effects of these procedures has been argued against, as DJB is not associated with changes in incretin signaling (Salinari et al., 2014), while inhibition of GLP-1 signaling has no effect on glycemia following RYGB (Jiménez et al., 2013; Shah et al., 2014) or in an operation similar to DJB (Troy et al., 2008). Further, GLP-1R KO models show no impairment in glycemic control (Mokadem et al., 2014). Thus, although compensation for the loss of GLP-1R function (in KO animals) could be a precipitating factor, improvement in glycemia following RYGB and DJB appears not to be dependent on GLP-1 signaling; however, it is possible that other gut peptides in the distal intestine may play a role.

As such, PYY has been implicated, as plasma PYY levels are also increased following RYGB (le Roux et al., 2006, 2007; Rodieux et al., 2008) and DJB (Imoto et al., 2014; Liu et al., 2012a; Liu et al., 2012b). While there is evidence for a causal link between PYY signaling and weight loss in both humans (le Roux et al., 2007; Morínigo et al., 2008) and rodents (Chandarana et al., 2011), studies investigating the role of PYY in the resolution of T2D are relatively lacking. A recent study, however, associates PYY with improved GLP-1 response and glucose tolerance (Chandarana et al., 2013) and suggests that studies aiming to investigate the role of PYY in the anti-diabetic effect of bariatric surgery are warranted.

Given the complexity and redundancy of postprandial intestinal signaling mechanisms, it is likely that the beneficial effects of gastric bypass cannot be solely attributed to changes in the action of a single peptide, but more likely from beneficial integrative adaptations involving an improved concerted action of gut sensing and signaling pathways. Thus, it was hypothesized that the success of bariatric surgery is partly due to the overall effectiveness of jejunal nutrient-sensing mechanisms, as intrajejunal infusion of glucose and lipids lowers HGP through a neuronal network as observed in the duodenum (Breen et al., 2012) (Figure 2). To evaluate the role of jejunal nutrient sensing in mediating the improvements in glycemia following bariatric

surgery independent of obesity, DJB surgery was performed on insulin-deficient, streptozodocin (STZ)-induced uncontrolled diabetic model and in Bio-breeding (BBdp) rats, an autoimmune type 1 diabetic rat. DJB rapidly (in 2 days) lowers plasma glucose concentrations in STZ-induced and BBdp diabetic rodents, and this glucose lowering is independent of changes in insulin concentrations, food intake, and body weight (Breen et al., 2012). This is in line with the fact that most studies demonstrate weight-loss-independent glycemic effects of DJB (Cohen et al., 2012b; Hu et al., 2013) and that DJB rapidly improves glucose tolerance but does not enhance insulin sensitivity (Jiao et al., 2013; Kindel et al., 2009). Importantly, during fasting-refeeding experiments, inhibition of jejunal glucose- and fatty-acid-sensing mechanisms via intrajejunal infusion of SGLT-1 inhibitor phlorizin or ACS inhibitor triacsin C, respectively, disrupts glucose homeostasis compared to vehicle infusions (Breen et al., 2012) (Figure 2). Thus, activation of jejunal nutrient-sensing mechanisms mediates the rapid glucose-lowering effect of DJB, likely via lowering of HGP through vagal signaling (Jiao et al., 2013). Similarly, improvement in glucose regulation following entero-gastro anastomosis (a variant of DJB) is mediated by a gut-brain neuronal axis that lowers glucose production (Troy et al., 2008).

It should be noted that while normalization of glucose concentrations in diabetic rats following DJB is associated with a rise in plasma GLP-1 levels, the effect in BBdp rats is independent of changes in GLP-1 (Breen et al., 2012); thus, the functional relevance of GLP-1 in mediating the rapid glucose-lowering effect induced by DJB remains to be clarified. As such, we have identified that another GI peptide, leptin, may be responsible for the rapid glucose-lowering effect observed during DJB (Rasmussen et al., 2014) (Figure 2). Although the main contributor to circulating leptin is adipocytes, leptin is also secreted by gastric chief cells in response to nutrients (Bado et al., 1998) and is subsequently detected in duodenal juices (Guilmeau et al., 2003). In fact, direct leptin infusion into the jejunum activates jejunal leptin receptor-PI3K signaling and lowers HGP via a neuronal network, while direct blockade of jejunal leptin receptor signaling disrupts glucose homeostasis in DJB-diabetic rodents during refeeding (Rasmussen et al., 2014). Although the specific intestinal cell type mediating the effect of leptin following DJB is not determined, recent evidence indicates that leptin receptors on vagal afferents innervating the intestine, but not intestinal epithelial cells themselves (de Lartigue et al., 2014; Rajala et al., 2014), are important for the development of obesity and possibly hyperglycemia. Thus, it is likely that jejunal leptin is directly activating the vagus nerve by binding to the leptin receptor localized on the afferents innervating the intestine (Burdyga et al., 2002).

Inhibition of jejunal leptin signaling does not disrupt glucose homeostasis to the same extent as seen in STZ-induced diabetic rodents who receive sham surgery (Rasmussen et al., 2014), indicating that complete normalization of blood glucose levels by DJB likely involves an integration of leptin signaling with both interactive and non-complimentary mechanisms. For example, leptin enhances CCK signaling via activating vagal leptin receptor (Barrachina et al., 1997; de Lartigue et al., 2010), while leptin may also mediate the anorectic effect of GLP-1 (Williams et al., 2006). Therefore, improved jejunal nutrient sensing (mentioned above) possibly via CCK or GLP-1 secretion may interact with jejunal leptin signaling to synergistically lower blood glucose levels (Figure 2), supporting a hypothesis of an improved action of multiple mechanisms in nutrient sensing. However, it is also possible that some of the rapid glucose normalizing effects of bariatric surgery are independent of jejunal nutrient and leptin signaling.

One candidate contributor to the effects of bariatric surgery is bile acid. Both RYGB (Kohli et al., 2013; Patti et al., 2009) and duodenal exclusion (via duodenal-endoluminal sleeve that blocks nutrient-tissue interaction in the duodenum) (Habegger et al., 2014a) alter the quantity and composition of bile acids, possibly through increased FGF19 signaling (Gerhard et al., 2013); however, early (1 week) improvement in glucose homeostasis is not associated with changes in bile acids or FGF19 (Jørgensen et al., 2015). Interestingly, vertical sleeve gastrectomy (VSG), which involves roughly 80% removal of the stomach while maintaining intestinal integrity, results in sustained weight reduction and improved glycemic control (Seeley et al., 2015), which is attributed not to changes in GLP-1 (Wilson-Pérez et al., 2013), ghrelin (Chambers et al., 2013), apo-IV (Pressler et al., 2015), or MC4R (Mul et al., 2012) signaling, but due to enhanced bile acid-FXR signaling (Ryan et al., 2014). It is interesting that despite leaving the intestine intact, VSG induces substantial enteroplasticity (Seeley et al., 2015), demonstrating the potential for future therapeutics to influence intestinal signaling mechanisms without intestinal surgical alteration. Of note, most studies examining improvement in glucose homeostasis following VSG are relatively long-term, with one study even demonstrating no difference in meal-stimulated glucose tolerance 1 week post-operatively (Peterli et al., 2009). Thus, a better understanding of how rapid and long-term anti-diabetic mechanisms adapt and interact with one another following bariatric surgery could provide crucial drug targets that may ultimately replace the need for surgical intervention.

Pharmacological Relevance of Small Intestinal Energy Sensory Mechanisms

Research demonstrating the intestinal tract is a salient contributor to both the physiological control of glucose metabolism and the beneficial outcomes of bariatric surgery highlights the gut as a potential therapeutic target. Indeed, several GLP-1 analogs are currently on the market for treatment of diabetes, namely exenatide and liraglutide, which share 53% and 97% homology with native GLP-1, respectively, and have proved successful in improving glycemia (Madsbad et al., 2008). The mechanisms detailing the glucose-lowering effect of these drugs have been extensively reviewed elsewhere (Campbell and Drucker, 2013), but it should be noted that in addition to a major incretin effect, evidence suggests GLP-1R agonists also lower HGP to control glucose metabolism (Abu-Hamdah et al., 2009), possibly via the aforementioned gut-brain-liver pathway. This opens up the possibility that other antidiabetic compounds that improve glucose homeostasis by lowering HGP may be gut mediated. In fact, a potential contributing role of small intestinal energy sensors to the HGP- and glucose-lowering effects of metformin and resveratrol has been recently evaluated (Côté et al., 2015; Duca et al., 2015) (Figure 3).

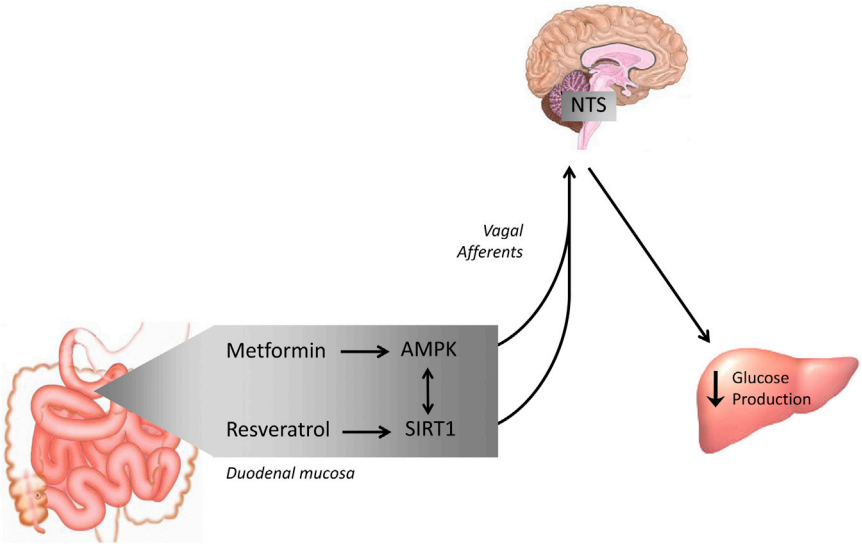

Figure 3. Metformin and Resveratrol Activate Duodenal Energy Sensors to Lower Glucose Production via a Neuronal Network
Metformin activates a duodenal AMPK-dependent, while resveratrol activates a duodenal SIRT1-dependent, neuronal pathway to lower HGP. AMPK, AMP-activated protein kinase; SIRT1, sirtuin 1; NTS, nucleus tractus solitarius.

Metformin

Metformin is the first-line therapeutic for T2D and lowers plasma glucose levels by inhibiting HGP (Foretz et al., 2014). Metformin was originally postulated to lower GP by indirectly activating hepatic AMP-activated kinase (AMPK), an intracellular energy sensor via increased AMP levels resultant from inhibition of the mitochondrial respiratory chain complex 1 (Owen et al., 2000). However, recent literature has challenged the conventional belief that metformin inhibits HGP via hepatic AMPK activation, demonstrating that metformin suppresses glycolytic enzymes in mice lacking liver AMPKα1/α2 (Foretz et al., 2010), antagonizes hepatic glucagon action (Miller et al., 2013), and/or alters mitochondrial and cytosolic redox states (Madiraju et al., 2014). Adding to, and complimenting, these described potential direct hepatic actions, preabsorptive metformin is recently documented to lower HGP in high-fat diet (HFD)-obese and diabetic rats via a neuronal network (Duca et al., 2015) (Figure 3), consistent with the fact that intraduodenal metformin, as opposed to intraportal or intravenous, infusion results in the greatest effect on lowering blood glucose levels (Stepensky et al., 2002). Specifically, preabsorptive metformin lowers HGP by activating duodenal mucosal AMPK and triggering GLP-1R (Duca et al., 2015), strengthening the hypothesis that an increase of GLP-1 levels mediates the antidiabetic effect of metformin (Maida et al., 2011; Vardarli et al., 2014).

Although it remains to be tested, it is plausible that metformin acts directly on GLP-1-secreting cells localized in the duodenum (Habib et al., 2012), since metformin-induced reduction of HGP is attenuated with intraduodenal infusion of GLP-1 receptor antagonist exendin-9 (Duca et al., 2015), despite metformin inducing GLP-1 release via a neuronal-hormonal reflex (Mulherin et al., 2011). Metformin may increase duodenal AMPK activity in the GLP-1-secreting cells, which induces calcium influx and GLP-1 release, similar to the fact that AMPK activates neuropeptide Y neurons via calcium influx (Kohno et al., 2011). Another AMPK activator, AICAR, increases GLP-1 (Maida et al., 2011; Mulherin et al., 2011), further suggesting that AMPK activation mediates GLP-1 release in EECs. Future studies are warranted to elucidate the underlying mechanisms of metformin-mediated increases in GLP-1 levels.

Of note, the physiological contribution of duodenal AMPK in the glucose-lowering effect of metformin is documented in an experimental setting where the pancreatic-euglycemic clamp is not performed. Specifically, diabetic rats with virally duodenal-targeted molecular inhibition of AMPK activity fail to exhibit lower plasma glucose levels in the first 60 min following an intragastric bolus injection of metformin, as compared to rats with intact duodenal AMPK (Duca et al., 2015), indicating a physiological glucose-lowering ability of duodenal metformin-AMPK signaling. Further, while both sets of rats (with inhibited or intact duodenal AMPK activity) exhibit overall reduction in plasma glucose levels 3 hr after the metformin gastric injection, the total drop in glucose in the rats with duodenal AMPK inhibition was only ~50% of that of rats with intact duodenal AMPK activity (Duca et al., 2015). Thus, the preabsorptive metformin-duodenal AMPK-induced reduction in plasma glucose levels has a potent and sustained contribution to the overall suppression of plasma glucose following metformin treatment.

Resveratrol

Metabolic improvements associated with activation of AMPK in various tissues involve an interactive dependency with another energy sensor, the NAD^+-dependent deacetylase sirtuin 1 (SIRT1) (Cantó et al., 2009; Côté et al., 2015; Feige et al., 2008; Fulco et al., 2008; Hou et al., 2008; Lan et al., 2008; Price et al., 2012). Resveratrol, a polyphenolic compound synthesized in plants, activates SIRT1, exerting caloric mimetic effects such as reducing plasma glucose levels and improving insulin sensitivity (Baur et al., 2006; Lagouge et al., 2006; Park et al., 2012; Price et al., 2012; Timmers et al., 2011), although the effectiveness in humans is debated (Bitterman and Chung, 2015). The underlying mechanisms remain elusive. In this regard, it is recently documented that intraduodenal infusion of resveratrol activates duodenal SIRT1 and triggers a vagal gut-brain neuronal axis to improve hypothalamic insulin sensitivity to lower HGP in HFD-fed and diabetic rodents (Côté et al., 2015) (Figure 3). This effect of resveratrol was duodenal AMPK dependent as well (Côté et al., 2015), and the possibility that duodenal SIRT1 is activated by the ability of AMPK to increase NAD^+ (Cantó et al., 2009; Feige et al., 2008; Fulco et al., 2008) remains to be tested.

Potential drugs targeting duodenal AMPK- and SIRT1-dependent pathways would add to an expanding list of potential "gut-targeted" treatments for diabetes. For example, although DPP-4

inhibitors get into systemic circulation and likely facilitate the direct action of endogenous GLP-1 on β-cells, a very low oral dose of sitagliptin (a DPP-4 inhibitor) selectively reduces intestinal DPP-4 activity and is sufficient to improve glucose tolerance in association with increased vagal nerve activity in diet-induced obese rodents (Waget et al., 2011). Two recent independent studies also demonstrate that intestinal-specific acting compounds, such as the anti-inflammatory agent 5-aminosalicylic acid (Luck et al., 2015) and a gut-restricted FXR agonist (Fang et al., 2015), improve whole-body metabolic homeostasis in obese rodents.

In summary, emerging studies are indicating that sensory mechanisms in the small intestine are pharmacologically and therapeutically relevant.

Conclusion

The traditional islet/insulin-centered model for glucose homeostasis has been recently challenged by the glucoregulatory importance of both the brain and insulin-independent mechanisms. Thus, a two-compartment model whereupon diabetes develops from a cooperative failure of both islet- and brain-centered-glucoregulatory systems is proposed (Schwartz et al., 2013). However, as highlighted in this perspective, intestinal nutrient sensing plays a physiological role in the maintenance of blood glucose levels by regulating HGP, and these signaling pathways are rapidly diminished with high-fat feeding (Cheung et al., 2009; Wang et al., 2008). Perhaps early perturbations in intestinal physiology during high-fat feeding precede the deleterious effect of a HFD on the glucoregulatory function of both the brain and pancreas, although this hypothesis remains to be examined. Nonetheless, as evidence continues to emerge, we propose that the GI tract should be incorporated into this 21st century model of glucose homeostasis, remotely activating brain-centered glucoregulatory systems.

There is controversy as to whether central glucoregulatory pathways are physiologically relevant in larger mammals (dogs and humans), in which some suggest glucose homeostasis is largely attributed to direct hepatic insulin action (Ramnanan et al., 2012), although recent studies challenge the overall glycemic importance of hepatic insulin signaling (O-Sullivan et al., 2015; Titchenell et al., 2015) and demonstrate that the brain can potently increase glucose effectiveness, which is insulin independent (Morton et al., 2013). Furthermore, in humans, oral diazoxide, a KATP channel activator, decreases HGP, likely via KATP channel activation in the brain, consistent with the fact that, in rodents, central blockade of the KATP channel abolishes the effect of oral diazoxide (Kishore et al., 2011). Additionally, in type 1 diabetics, 6 months of diazoxide treatment improves metabolic control independent of changes in insulin production, possibly due to the aforementioned mechanism (Radtke et al., 2010), while intranasal insulin delivery reduces HGP in healthy men (Dash et al., 2015). The potential mechanisms for the brain to control HGP are reviewed elsewhere (Carey et al., 2013), but it should be noted that intranasal insulin delivery in humans increases hypothalamic activity, parasympathetic tone, and whole-body insulin sensitivity, indicating a potential hypothalamic-vagal efferent axis regulating glucose homeostasis (Heni et al., 2014). This is consistent with both rodent findings (Pocai et al., 2005) and the fact that activation of muscarinic receptors inhibits HGP in humans (Boyle et al., 1988). Although hepatic denervation in humans with liver transplants does not impair glucose homeostasis (Perseghin et al., 1997), the loss of parasympathetic drive may be off-set by the lack of opposing sympathetic activity (Cailotto et al., 2008). Clearly, while rodent studies and recent clinical data depict the glucoregulatory role of the brain- and gut-brain-liver axis, future clinical studies exploring these pathways are warranted.

Perhaps more crucial than outlining the physiological impact of these axes is the pressing need for the development and better understanding of successful antidiabetic treatment options. This perspective highlights the vital role of the small intestinal energy sensory mechanisms in the anti-diabetic effect of bariatric surgery, metformin, and resveratrol. Interestingly, one common link between these surgical and pharmacological interventions is alterations in the gut microbiota (Dao et al., 2011; Shin et al., 2014; Zhang et al., 2009). As the gut microbiota rapidly adapts to its environment, shifts in the bacterial communities of the GI tract may represent the initial trigger for the metabolic improvements observed following these surgical and pharmacological treatments, indicating the potential significance of being able to manipulate the gut microbiota. As we better understand how gut microbial-host crosstalk could mediate host metabolic changes, we may one day be able to identify or create specific bacterial therapy that could target intestinal energy sensory mechanisms that regulate glucose homeostasis as those described throughout the review, and preliminary evidence suggests microbiota transplant could be a successful antidiabetic treatment (Vrieze et al., 2012). Overall, the GI tract represents a promising avenue for the development of successful targeted therapeutic options for the treatment of diabetes.

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REFERENCES

Abu-Hamdah, R., Rabiee, A., Meneilly, G.S., Shannon, R.P., Andersen, D.K., and Elahi, D. (2009). Clinical review: The extrapancreatic effects of glucagon-like peptide-1 and related peptides. J. Clin. Endocrinol. Metab. *94*, 1843–1852.

Amato, A., Cinci, L., Rotondo, A., Serio, R., Faussone-Pellegrini, M.S., Vannucchi, M.G., and Mulè, F. (2010). Peripheral motor action of glucagon-like peptide-1 through enteric neuronal receptors. Neurogastroenterol. Motil. *22*, 664–e203.

Bado, A., Levasseur, S., Attoub, S., Kermorgant, S., Laigneau, J.P., Bortoluzzi, M.N., Moizo, L., Lehy, T., Guerre-Millo, M., Le Marchand-Brustel, Y., and Lewin, M.J. (1998). The stomach is a source of leptin. Nature *394*, 790–793.

Baggio, L.L., Huang, Q., Brown, T.J., and Drucker, D.J. (2004). Oxyntomodulin and glucagon-like peptide-1 differentially regulate murine food intake and energy expenditure. Gastroenterology *127*, 546–558.

Barrachina, M.D., Martínez, V., Wang, L., Wei, J.Y., and Taché, Y. (1997). Synergistic interaction between leptin and cholecystokinin to reduce short-term food intake in lean mice. Proc. Natl. Acad. Sci. USA *94*, 10455–10460.

Baur, J.A., Pearson, K.J., Price, N.L., Jamieson, H.A., Lerin, C., Kalra, A., Prabhu, V.V., Allard, J.S., Lopez-Lluch, G., Lewis, K., et al. (2006). Resveratrol improves health and survival of mice on a high-calorie diet. Nature *444*, 337–342.

Beglinger, C., Degen, L., Matzinger, D., D'Amato, M., and Drewe, J. (2001). Loxiglumide, a CCK-A receptor antagonist, stimulates calorie intake and hunger feelings in humans. Am. J. Physiol. Regul. Integr. Comp. Physiol. *280*, R1149–R1154.

Bellissimo, N., and Anderson, G.H. (2003). Cholecystokinin-A receptors are involved in food intake suppression in rats after intake of all fats and carbohydrates tested. J. Nutr. *133*, 2319–2325.

Berthoud, H.R., Kressel, M., Raybould, H.E., and Neuhuber, W.L. (1995). Vagal sensors in the rat duodenal mucosa: distribution and structure as revealed by in vivo DiI-tracing. Anat. Embryol. (Berl.) *191*, 203–212.

Bi, S., Chen, J., Behles, R.R., Hyun, J., Kopin, A.S., and Moran, T.H. (2007). Differential body weight and feeding responses to high-fat diets in rats and mice lacking cholecystokinin 1 receptors. Am. J. Physiol. Regul. Integr. Comp. Physiol. *293*, R55–R63.

Bitterman, J.L., and Chung, J.H. (2015). Metabolic effects of resveratrol: addressing the controversies. Cell. Mol. Life Sci. *72*, 1473–1488.

Blevins, J.E., Overduin, J., Fuller, J.M., Cummings, D.E., Matsumoto, K., and Moralejo, D.H. (2009). Normal feeding and body weight in Fischer 344 rats lacking the cholecystokinin-1 receptor gene. Brain Res. *1255*, 98–112.

Blouet, C., and Schwartz, G.J. (2012). Duodenal lipid sensing activates vagal afferents to regulate non-shivering brown fat thermogenesis in rats. PLoS ONE *7*, e51898.

Boyle, P.J., Liggett, S.B., Shah, S.D., and Cryer, P.E. (1988). Direct muscarinic cholinergic inhibition of hepatic glucose production in humans. J. Clin. Invest. *82*, 445–449.

Breen, D.M., Yue, J.T., Rasmussen, B.A., Kokorovic, A., Cheung, G.W., and Lam, T.K. (2011). Duodenal PKC-δ and cholecystokinin signaling axis regulates glucose production. Diabetes *60*, 3148–3153.

Breen, D.M., Rasmussen, B.A., Kokorovic, A., Wang, R., Cheung, G.W., and Lam, T.K. (2012). Jejunal nutrient sensing is required for duodenal-jejunal bypass surgery to rapidly lower glucose concentrations in uncontrolled diabetes. Nat. Med. *18*, 950–955.

Burcelin, R., Da Costa, A., Drucker, D., and Thorens, B. (2001). Glucose competence of the hepatoportal vein sensor requires the presence of an activated glucagon-like peptide-1 receptor. Diabetes *50*, 1720–1728.

Burdyga, G., Spiller, D., Morris, R., Lal, S., Thompson, D.G., Saeed, S., Dimaline, R., Varro, A., and Dockray, G.J. (2002). Expression of the leptin receptor in rat and human nodose ganglion neurones. Neuroscience *109*, 339–347.

Cailotto, C., van Heijningen, C., van der Vliet, J., van der Plasse, G., Habold, C., Kalsbeek, A., Pévet, P., and Buijs, R.M. (2008). Daily rhythms in metabolic liver enzymes and plasma glucose require a balance in the autonomic output to the liver. Endocrinology *149*, 1914–1925.

Campbell, J.E., and Drucker, D.J. (2013). Pharmacology, physiology, and mechanisms of incretin hormone action. Cell Metab. *17*, 819–837.

Campos, C.A., Wright, J.S., Czaja, K., and Ritter, R.C. (2012). CCK-induced reduction of food intake and hindbrain MAPK signaling are mediated by NMDA receptor activation. Endocrinology *153*, 2633–2646.

Cantó, C., Gerhart-Hines, Z., Feige, J.N., Lagouge, M., Noriega, L., Milne, J.C., Elliott, P.J., Puigserver, P., and Auwerx, J. (2009). AMPK regulates energy expenditure by modulating NAD+ metabolism and SIRT1 activity. Nature *458*, 1056–1060.

Carey, M., Kehlenbrink, S., and Hawkins, M. (2013). Evidence for central regulation of glucose metabolism. J. Biol. Chem. *288*, 34981–34988.

Caspi, L., Wang, P.Y., and Lam, T.K. (2007). A balance of lipid-sensing mechanisms in the brain and liver. Cell Metab. *6*, 99–104.

Cawston, E.E., and Miller, L.J. (2010). Therapeutic potential for novel drugs targeting the type 1 cholecystokinin receptor. Br. J. Pharmacol. *159*, 1009–1021.

Chambers, A.P., Jessen, L., Ryan, K.K., Sisley, S., Wilson-Pérez, H.E., Stefater, M.A., Gaitonde, S.G., Sorrell, J.E., Toure, M., Berger, J., et al. (2011). Weight-independent changes in blood glucose homeostasis after gastric bypass or vertical sleeve gastrectomy in rats. Gastroenterology *141*, 950–958.

Chambers, A.P., Kirchner, H., Wilson-Perez, H.E., Willency, J.A., Hale, J.E., Gaylinn, B.D., Thorner, M.O., Pfluger, P.T., Gutierrez, J.A., Tschop, M.H., et al. (2013). The effects of vertical sleeve gastrectomy in rodents are ghrelin independent. Gastroenterology *144*, http://dx.doi.org/10.1053/j.gastro.2012.09.009.

Chandarana, K., Gelegen, C., Karra, E., Choudhury, A.I., Drew, M.E., Fauveau, V., Viollet, B., Andreelli, F., Withers, D.J., and Batterham, R.L. (2011). Diet and gastrointestinal bypass-induced weight loss: the roles of ghrelin and peptide YY. Diabetes *60*, 810–818.

Chandarana, K., Gelegen, C., Irvine, E.E., Choudhury, A.I., Amouyal, C., Andreelli, F., Withers, D.J., and Batterham, R.L. (2013). Peripheral activation of the Y2-receptor promotes secretion of GLP-1 and improves glucose tolerance. Mol. Metab. *2*, 142–152.

Chang, C.H., Chey, W.Y., and Chang, T.M. (2000). Cellular mechanism of sodium oleate-stimulated secretion of cholecystokinin and secretin. Am. J. Physiol. Gastrointest. Liver Physiol. *279*, G295–G303.

Cheung, G.W., Kokorovic, A., Lam, C.K., Chari, M., and Lam, T.K. (2009). Intestinal cholecystokinin controls glucose production through a neuronal network. Cell Metab. *10*, 99–109.

Cohen, R.V., Schiavon, C.A., Pinheiro, J.S., Correa, J.L., and Rubino, F. (2007). Duodenal-jejunal bypass for the treatment of type 2 diabetes in patients with body mass index of 22-34 kg/m2: a report of 2 cases. Surg. Obes. Relat. Dis. *3*, 195–197.

Cohen, R.V., Pinheiro, J.C., Schiavon, C.A., Salles, J.E., Wajchenberg, B.L., and Cummings, D.E. (2012a). Effects of gastric bypass surgery in patients with type 2 diabetes and only mild obesity. Diabetes Care *35*, 1420–1428.

Cohen, R.V., Rubino, F., Schiavon, C., and Cummings, D.E. (2012b). Diabetes remission without weight loss after duodenal bypass surgery. Surg. Obes. Relat. Dis. *8*, e66–e68.

Corssmit, E.P., Van Lanschot, J.J., Romijn, J.A., Endert, E., and Sauerwein, H.P. (1995). Truncal vagotomy does not affect postabsorptive glucose metabolism in humans. J. Appl. Physiol. *79*, 97–101.

Costa, M., Brookes, S.J., and Hennig, G.W. (2000). Anatomy and physiology of the enteric nervous system. Gut *47 Suppl 4*, iv15–iv19.

Côté, C.D., Zadeh-Tahmasebi, M., Rasmussen, B.A., Duca, F.A., and Lam, T.K. (2014). Hormonal signaling in the gut. J. Biol. Chem. *289*, 11642–11649.

Côté, C.D., Rasmussen, B.A., Duca, F.A., Zadeh-Tahmasebi, M., Baur, J.A., Daljeet, M., Breen, D.M., Filippi, B.M., and Lam, T.K. (2015). Resveratrol activates duodenal Sirt1 to reverse insulin resistance in rats through a neuronal network. Nat. Med. *21*, 498–505.

Cummings, D.E., and Overduin, J. (2007). Gastrointestinal regulation of food intake. J. Clin. Invest. *117*, 13–23.

Dao, T.M., Waget, A., Klopp, P., Serino, M., Vachoux, C., Pechere, L., Drucker, D.J., Champion, S., Barthélemy, S., Barra, Y., et al. (2011). Resveratrol increases glucose induced GLP-1 secretion in mice: a mechanism which contributes to the glycemic control. PLoS ONE *6*, e20700.

Dar, M.S., Chapman, W.H., 3rd, Pender, J.R., Drake, A.J., 3rd, O'Brien, K., Tanenberg, R.J., Dohm, G.L., and Pories, W.J. (2012). GLP-1 response to a mixed meal: what happens 10 years after Roux-en-Y gastric bypass (RYGB)? Obes. Surg. *22*, 1077–1083.

Darling, R.A., Zhao, H., Kinch, D., Li, A.J., Simasko, S.M., and Ritter, S. (2014). Mercaptoacetate and fatty acids exert direct and antagonistic effects on nodose neurons via GPR40 fatty acid receptors. Am. J. Physiol. Regul. Integr. Comp. Physiol. *307*, R35–R43.

Dash, S., Xiao, C., Morgantini, C., Koulajian, K., and Lewis, G.F. (2015). Intranasal insulin suppresses endogenous glucose production in humans compared with placebo in the presence of similar venous insulin concentrations. Diabetes *64*, 766–774.

de Lartigue, G., Lur, G., Dimaline, R., Varro, A., Raybould, H., and Dockray, G.J. (2010). EGR1 Is a target for cooperative interactions between cholecystokinin and leptin, and inhibition by ghrelin, in vagal afferent neurons. Endocrinology *151*, 3589–3599.

de Lartigue, G., Ronveaux, C.C., and Raybould, H.E. (2014). Deletion of leptin signaling in vagal afferent neurons results in hyperphagia and obesity. Mol. Metab. *3*, 595–607.

Dirksen, C., Jørgensen, N.B., Bojsen-Møller, K.N., Kielgast, U., Jacobsen, S.H., Clausen, T.R., Worm, D., Hartmann, B., Rehfeld, J.F., Damgaard, M., et al. (2013). 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. (Lond) *37*, 1452–1459.

Dobbins, R.L., Greenway, F.L., Chen, L., Liu, Y., Breed, S.L., Andrews, S.M., Wald, J.A., Walker, A.C., and Smith, C.D. (2015). Selective sodium-dependent glucose transporter 1 inhibitors block glucose absorption and impair glucose-dependent insulinotropic peptide release. Am. J. Physiol. Gastrointest. Liver Physiol. *308*, G946–G954.

Dockray, G.J. (2013). Enteroendocrine cell signalling via the vagus nerve. Curr. Opin. Pharmacol. *13*, 954–958.

Duca, F.A., and Yue, J.T. (2014). Fatty acid sensing in the gut and the hypothalamus: in vivo and in vitro perspectives. Mol. Cell. Endocrinol. *397*, 23–33.

Duca, F.A., Côté, C.D., Rasmussen, B.A., Zadeh-Tahmasebi, M., Rutter, G.A., Filippi, B.M., and Lam, T.K. (2015). Metformin activates a duodenal Ampk-dependent pathway to lower hepatic glucose production in rats. Nat. Med. *21*, 506–511.

Edfalk, S., Steneberg, P., and Edlund, H. (2008). Gpr40 is expressed in enteroendocrine cells and mediates free fatty acid stimulation of incretin secretion. Diabetes *57*, 2280–2287.

Edwards, C.M., Todd, J.F., Mahmoudi, M., Wang, Z., Wang, R.M., Ghatei, M.A., and Bloom, S.R. (1999). Glucagon-like peptide 1 has a physiological role in the control of postprandial glucose in humans: studies with the antagonist exendin 9-39. Diabetes *48*, 86–93.

Fang, S., Suh, J.M., Reilly, S.M., Yu, E., Osborn, O., Lackey, D., Yoshihara, E., Perino, A., Jacinto, S., Lukasheva, Y., et al. (2015). Intestinal FXR agonism promotes adipose tissue browning and reduces obesity and insulin resistance. Nat. Med. *21*, 159–165.

Feige, J.N., Lagouge, M., Canto, C., Strehle, A., Houten, S.M., Milne, J.C., Lambert, P.D., Mataki, C., Elliott, P.J., and Auwerx, J. (2008). Specific SIRT1 activation mimics low energy levels and protects against diet-induced metabolic disorders by enhancing fat oxidation. Cell Metab. *8*, 347–358.

Foretz, M., Hébrard, S., Leclerc, J., Zarrinpashneh, E., Soty, M., Mithieux, G., Sakamoto, K., Andreelli, F., and Viollet, B. (2010). Metformin inhibits hepatic gluconeogenesis in mice independently of the LKB1/AMPK pathway via a decrease in hepatic energy state. J. Clin. Invest. *120*, 2355–2369.

Foretz, M., Guigas, B., Bertrand, L., Pollak, M., and Viollet, B. (2014). Metformin: from mechanisms of action to therapies. Cell Metab. *20*, 953–966.

Fulco, M., Cen, Y., Zhao, P., Hoffman, E.P., McBurney, M.W., Sauve, A.A., and Sartorelli, V. (2008). Glucose restriction inhibits skeletal myoblast differentiation by activating SIRT1 through AMPK-mediated regulation of Nampt. Dev. Cell *14*, 661–673.

Gerhard, G.S., Styer, A.M., Wood, G.C., Roesch, S.L., Petrick, A.T., Gabrielsen, J., Strodel, W.E., Still, C.D., and Argyropoulos, G. (2013). A role for fibroblast growth factor 19 and bile acids in diabetes remission after Roux-en-Y gastric bypass. Diabetes Care *36*, 1859–1864.

Gorboulev, V., Schürmann, A., Vallon, V., Kipp, H., Jaschke, A., Klessen, D., Friedrich, A., Scherneck, S., Rieg, T., Cunard, R., et al. (2012). Na(+)-D-glucose cotransporter SGLT1 is pivotal for intestinal glucose absorption and glucose-dependent incretin secretion. Diabetes *61*, 187–196.

Guilmeau, S., Buyse, M., Tsocas, A., Laigneau, J.P., and Bado, A. (2003). Duodenal leptin stimulates cholecystokinin secretion: evidence of a positive leptin-cholecystokinin feedback loop. Diabetes *52*, 1664–1672.

Habegger, K.M., Al-Massadi, O., Heppner, K.M., Myronovych, A., Holland, J., Berger, J., Yi, C.X., Gao, Y., Lehti, M., Ottaway, N., et al. (2014a). Duodenal nutrient exclusion improves metabolic syndrome and stimulates villus hyperplasia. Gut *63*, 1238–1246.

Habegger, K.M., Heppner, K.M., Amburgy, S.E., Ottaway, N., Holland, J., Raver, C., Bartley, E., Müller, T.D., Pfluger, P.T., Berger, J., et al. (2014b). GLP-1R responsiveness predicts individual gastric bypass efficacy on glucose tolerance in rats. Diabetes *63*, 505–513.

Habib, A.M., Richards, P., Cairns, L.S., Rogers, G.J., Bannon, C.A., Parker, H.E., Morley, T.C., Yeo, G.S., Reimann, F., and Gribble, F.M. (2012). Overlap of endocrine hormone expression in the mouse intestine revealed by transcriptional profiling and flow cytometry. Endocrinology *153*, 3054–3065.

Hayes, M.R., De Jonghe, B.C., and Kanoski, S.E. (2010). Role of the glucagon-like-peptide-1 receptor in the control of energy balance. Physiol. Behav. *100*, 503–510.

Hayes, M.R., Kanoski, S.E., De Jonghe, B.C., Leichner, T.M., Alhadeff, A.L., Fortin, S.M., Arnold, M., Langhans, W., and Grill, H.J. (2011). The common hepatic branch of the vagus is not required to mediate the glycemic and food intake suppressive effects of glucagon-like-peptide-1. Am. J. Physiol. Regul. Integr. Comp. Physiol. *301*, R1479–R1485.

He, W., Lam, T.K., Obici, S., and Rossetti, L. (2006). Molecular disruption of hypothalamic nutrient sensing induces obesity. Nat. Neurosci. *9*, 227–233.

Heni, M., Wagner, R., Kullmann, S., Veit, R., Mat Husin, H., Linder, K., Benkendorff, C., Peter, A., Stefan, N., Häring, H.U., et al. (2014). Central insulin administration improves whole-body insulin sensitivity via hypothalamus and parasympathetic outputs in men. Diabetes *63*, 4083–4088.

Hirasawa, A., Tsumaya, K., Awaji, T., Katsuma, S., Adachi, T., Yamada, M., Sugimoto, Y., Miyazaki, S., and Tsujimoto, G. (2005). Free fatty acids regulate gut incretin glucagon-like peptide-1 secretion through GPR120. Nat. Med. *11*, 90–94.

Holst, J.J. (2007). The physiology of glucagon-like peptide 1. Physiol. Rev. *87*, 1409–1439.

Hou, X., Xu, S., Maitland-Toolan, K.A., Sato, K., Jiang, B., Ido, Y., Lan, F., Walsh, K., Wierzbicki, M., Verbeuren, T.J., et al. (2008). SIRT1 regulates hepatocyte lipid metabolism through activating AMP-activated protein kinase. J. Biol. Chem. *283*, 20015–20026.

Hu, C., Zhang, G., Sun, D., Han, H., and Hu, S. (2013). Duodenal-jejunal bypass improves glucose metabolism and adipokine expression independently of weight loss in a diabetic rat model. Obes. Surg. *23*, 1436–1444.

Hu, C., Su, Q., Li, F., Zhang, G., Sun, D., Han, H., Liu, S., and Hu, S. (2014). Duodenal-Jejunal bypass improves glucose homeostasis in association with decreased proinflammatory response and activation of JNK in the liver and adipose tissue in a T2DM rat model. Obes. Surg. *24*, 1453–1462.

Humphrey, C.S., Dykes, J.R., and Johnston, D. (1975). Effects of truncal, selective, and highly selective vagotomy on glucose tolerance and insulin secretion in patients with duodenal ulcer. Part II-Comparison of response to oral and intravenous glucose. BMJ *2*, 114–116.

Ikramuddin, S., Korner, J., Lee, W.J., Connett, J.E., Inabnet, W.B., Billington, C.J., Thomas, A.J., Leslie, D.B., Chong, K., Jeffery, R.W., et al. (2013). Roux-en-Y gastric bypass vs intensive medical management for the control of type 2 diabetes, hypertension, and hyperlipidemia: the Diabetes Surgery Study randomized clinical trial. JAMA *309*, 2240–2249.

Imoto, H., Shibata, C., Ikezawa, F., Kikuchi, D., Someya, S., Miura, K., Naitoh, T., and Unno, M. (2014). Effects of duodeno-jejunal bypass on glucose metabolism in obese rats with type 2 diabetes. Surg. Today *44*, 340–348.

Jiao, J., Bae, E.J., Bandyopadhyay, G., Oliver, J., Marathe, C., Chen, M., Hsu, J.Y., Chen, Y., Tian, H., Olefsky, J.M., and Saberi, M. (2013). Restoration of euglycemia after duodenal bypass surgery is reliant on central and peripheral inputs in Zucker fa/fa rats. Diabetes *62*, 1074–1083.

Jiménez, A., Casamitjana, R., Viaplana-Masclans, J., Lacy, A., and Vidal, J. (2013). GLP-1 action and glucose tolerance in subjects with remission of type 2 diabetes after gastric bypass surgery. Diabetes Care *36*, 2062–2069.

Jørgensen, N.B., Dirksen, C., Bojsen-Møller, K.N., Kristiansen, V.B., Wulff, B.S., Rainteau, D., Humbert, L., Rehfeld, J.F., Holst, J.J., Madsbad, S., and Clausen, T.R. (2015). Improvements in glucose metabolism early after gastric bypass surgery are not explained by increases in total bile acids and fibroblast growth factor 19 concentrations. J. Clin. Endocrinol. Metab. *100*, E396–E406.

Karlsson, J., Taft, C., Rydén, A., Sjöström, L., and Sullivan, M. (2007). Ten-year trends in health-related quality of life after surgical and conventional treatment

for severe obesity: the SOS intervention study. Int J Obes (Lond) *31*, 1248–1261.

Kawano, K., Hirashima, T., Mori, S., Saitoh, Y., Kurosumi, M., and Natori, T. (1992). Spontaneous long-term hyperglycemic rat with diabetic complications. Otsuka Long-Evans Tokushima Fatty (OLETF) strain. Diabetes *41*, 1422–1428.

Kindel, T.L., Yoder, S.M., Seeley, R.J., D'Alessio, D.A., and Tso, P. (2009). Duodenal-jejunal exclusion improves glucose tolerance in the diabetic, Goto-Kakizaki rat by a GLP-1 receptor-mediated mechanism. J. Gastrointest. Surg. *13*, 1762–1772.

Kishore, P., Boucai, L., Zhang, K., Li, W., Koppaka, S., Kehlenbrink, S., Schiwek, A., Esterson, Y.B., Mehta, D., Bursheh, S., et al. (2011). Activation of K(ATP) channels suppresses glucose production in humans. J. Clin. Invest. *121*, 4916–4920.

Koda, S., Date, Y., Murakami, N., Shimbara, T., Hanada, T., Toshinai, K., Niijima, A., Furuya, M., Inomata, N., Osuye, K., and Nakazato, M. (2005). The role of the vagal nerve in peripheral PYY3-36-induced feeding reduction in rats. Endocrinology *146*, 2369–2375.

Kohli, R., Bradley, D., Setchell, K.D., Eagon, J.C., Abumrad, N., and Klein, S. (2013). Weight loss induced by Roux-en-Y gastric bypass but not laparoscopic adjustable gastric banding increases circulating bile acids. J. Clin. Endocrinol. Metab. *98*, E708–E712.

Kohno, D., Sone, H., Tanaka, S., Kurita, H., Gantulga, D., and Yada, T. (2011). AMP-activated protein kinase activates neuropeptide Y neurons in the hypothalamic arcuate nucleus to increase food intake in rats. Neurosci. Lett. *499*, 194–198.

Kokorovic, A., Cheung, G.W., Breen, D.M., Chari, M., Lam, C.K., and Lam, T.K. (2011). Duodenal mucosal protein kinase C-δ regulates glucose production in rats. Gastroenterology *141*, 1720–1727.

Kolligs, F., Fehmann, H.C., Göke, R., and Göke, B. (1995). Reduction of the incretin effect in rats by the glucagon-like peptide 1 receptor antagonist exendin (9-39) amide. Diabetes *44*, 16–19.

Lagouge, M., Argmann, C., Gerhart-Hines, Z., Meziane, H., Lerin, C., Daussin, F., Messadeq, N., Milne, J., Lambert, P., Elliott, P., et al. (2006). Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell *127*, 1109–1122.

Lan, F., Cacicedo, J.M., Ruderman, N., and Ido, Y. (2008). SIRT1 modulation of the acetylation status, cytosolic localization, and activity of LKB1. Possible role in AMP-activated protein kinase activation. J. Biol. Chem. *283*, 27628–27635.

le Roux, C.W., Aylwin, S.J., Batterham, R.L., Borg, C.M., Coyle, F., Prasad, V., Shurey, S., Ghatei, M.A., Patel, A.G., and Bloom, S.R. (2006). Gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters. Ann. Surg. *243*, 108–114.

le Roux, C.W., Welbourn, R., Werling, M., Osborne, A., Kokkinos, A., Laurenius, A., Lönroth, H., Fändriks, L., Ghatei, M.A., Bloom, S.R., and Olbers, T. (2007). Gut hormones as mediators of appetite and weight loss after Roux-en-Y gastric bypass. Ann. Surg. *246*, 780–785.

Lee, H.C., Kim, M.K., Kwon, H.S., Kim, E., and Song, K.H. (2010). Early changes in incretin secretion after laparoscopic duodenal-jejunal bypass surgery in type 2 diabetic patients. Obes. Surg. *20*, 1530–1535.

Liou, A.P., Sei, Y., Zhao, X., Feng, J., Lu, X., Thomas, C., Pechhold, S., Raybould, H.E., and Wank, S.A. (2011). The extracellular calcium-sensing receptor is required for cholecystokinin secretion in response to L-phenylalanine in acutely isolated intestinal I cells. Am. J. Physiol. Gastrointest. Liver Physiol. *300*, G538–G546.

Liu, S., Zhang, G., Wang, L., Sun, D., Chen, W., Yan, Z., Sun, Y., and Hu, S. (2012a). The entire small intestine mediates the changes in glucose homeostasis after intestinal surgery in Goto-Kakizaki rats. Ann. Surg. *256*, 1049–1058.

Liu, S.Z., Sun, D., Zhang, G.Y., Wang, L., Liu, T., Sun, Y., Li, M.X., and Hu, S.Y. (2012b). A high-fat diet reverses improvement in glucose tolerance induced by duodenal-jejunal bypass in type 2 diabetic rats. Chin. Med. J. (Engl.) *125*, 912–919.

Lo, C.M., Zhang, D.M., Pearson, K., Ma, L., Sun, W., Sakai, R.R., Davidson, W.S., Liu, M., Raybould, H.E., Woods, S.C., and Tso, P. (2007). Interaction of apolipoprotein AIV with cholecystokinin on the control of food intake. Am. J. Physiol. Regul. Integr. Comp. Physiol. *293*, R1490–R1494.

Lu, W.J., Yang, Q., Yang, L., Lee, D., D'Alessio, D., and Tso, P. (2012). Chylomicron formation and secretion is required for lipid-stimulated release of incretins GLP-1 and GIP. Lipids *47*, 571–580.

Luck, H., Tsai, S., Chung, J., Clemente-Casares, X., Ghazarian, M., Revelo, X.S., Lei, H., Luk, C.T., Shi, S.Y., Surendra, A., et al. (2015). Regulation of obesity-related insulin resistance with gut anti-inflammatory agents. Cell Metab. *21*, 527–542.

Madiraju, A.K., Erion, D.M., Rahimi, Y., Zhang, X.M., Braddock, D.T., Albright, R.A., Prigaro, B.J., Wood, J.L., Bhanot, S., MacDonald, M.J., et al. (2014). Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. Nature *510*, 542–546.

Madsbad, S., Krarup, T., Deacon, C.F., and Holst, J.J. (2008). Glucagon-like peptide receptor agonists and dipeptidyl peptidase-4 inhibitors in the treatment of diabetes: a review of clinical trials. Curr. Opin. Clin. Nutr. Metab. Care *11*, 491–499.

Madsbad, S., Dirksen, C., and Holst, J.J. (2014). Mechanisms of changes in glucose metabolism and bodyweight after bariatric surgery. Lancet Diabetes Endocrinol. *2*, 152–164.

Maida, A., Lamont, B.J., Cao, X., and Drucker, D.J. (2011). Metformin regulates the incretin receptor axis via a pathway dependent on peroxisome proliferator-activated receptor-α in mice. Diabetologia *54*, 339–349.

Manning, S., Pucci, A., and Batterham, R.L. (2015). Roux-en-Y gastric bypass: effects on feeding behavior and underlying mechanisms. J. Clin. Invest. *125*, 939–948.

Marina, A.L., Utzschneider, K.M., Wright, L.A., Montgomery, B.K., Marcovina, S.M., and Kahn, S.E. (2012). Colesevelam improves oral but not intravenous glucose tolerance by a mechanism independent of insulin sensitivity and β-cell function. Diabetes Care *35*, 1119–1125.

Matozaki, T., and Williams, J.A. (1989). Multiple sources of 1,2-diacylglycerol in isolated rat pancreatic acini stimulated by cholecystokinin. Involvement of phosphatidylinositol bisphosphate and phosphatidylcholine hydrolysis. J. Biol. Chem. *264*, 14729–14734.

Miller, R.A., Chu, Q., Xie, J., Foretz, M., Viollet, B., and Birnbaum, M.J. (2013). Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. Nature *494*, 256–260.

Mingrone, G., Panunzi, S., De Gaetano, A., Guidone, C., Iaconelli, A., Leccesi, L., Nanni, G., Pomp, A., Castagneto, M., Ghirlanda, G., and Rubino, F. (2012). Bariatric surgery versus conventional medical therapy for type 2 diabetes. N. Engl. J. Med. *366*, 1577–1585.

Miras, A.D., and le Roux, C.W. (2013). Mechanisms underlying weight loss after bariatric surgery. Nat. Rev. Gastroenterol. Hepatol. *10*, 575–584.

Mokadem, M., Zechner, J.F., Margolskee, R.F., Drucker, D.J., and Aguirre, V. (2014). Effects of Roux-en-Y gastric bypass on energy and glucose homeostasis are preserved in two mouse models of functional glucagon-like peptide-1 deficiency. Mol. Metab. *3*, 191–201.

Morínigo, R., Vidal, J., Lacy, A.M., Delgado, S., Casamitjana, R., and Gomis, R. (2008). Circulating peptide YY, weight loss, and glucose homeostasis after gastric bypass surgery in morbidly obese subjects. Ann. Surg. *247*, 270–275.

Moriya, R., Shirakura, T., Ito, J., Mashiko, S., and Seo, T. (2009). Activation of sodium-glucose cotransporter 1 ameliorates hyperglycemia by mediating incretin secretion in mice. Am. J. Physiol. Endocrinol. Metab. *297*, E1358–E1365.

Morton, G.J., Matsen, M.E., Bracy, D.P., Meek, T.H., Nguyen, H.T., Stefanovski, D., Bergman, R.N., Wasserman, D.H., and Schwartz, M.W. (2013). FGF19 action in the brain induces insulin-independent glucose lowering. J. Clin. Invest. *123*, 4799–4808.

Mul, J.D., Begg, D.P., Alsters, S.I., van Haaften, G., Duran, K.J., D'Alessio, D.A., le Roux, C.W., Woods, S.C., Sandoval, D.A., Blakemore, A.I., et al. (2012). Effect of vertical sleeve gastrectomy in melanocortin receptor 4-deficient rats. Am. J. Physiol. Endocrinol. Metab. *303*, E103–E110.

Mulherin, A.J., Oh, A.H., Kim, H., Grieco, A., Lauffer, L.M., and Brubaker, P.L. (2011). Mechanisms underlying metformin-induced secretion of glucagon-like peptide-1 from the intestinal L cell. Endocrinology *152*, 4610–4619.

Mumphrey, M.B., Patterson, L.M., Zheng, H., and Berthoud, H.R. (2013). Roux-en-Y gastric bypass surgery increases number but not density of

CCK-, GLP-1-, 5-HT-, and neurotensin-expressing enteroendocrine cells in rats. Neurogastroenterol. Motil. *25*, e70–e79.

Nakabayashi, H., Nishizawa, M., Nakagawa, A., Takeda, R., and Niijima, A. (1996). Vagal hepatopancreatic reflex effect evoked by intraportal appearance of tGLP-1. Am. J. Physiol. *271*, E808–E813.

Nakagawa, A., Satake, H., Nakabayashi, H., Nishizawa, M., Furuya, K., Nakano, S., Kigoshi, T., Nakayama, K., and Uchida, K. (2004). Receptor gene expression of glucagon-like peptide-1, but not glucose-dependent insulinotropic polypeptide, in rat nodose ganglion cells. Auton. Neurosci. *110*, 36–43.

O-Sullivan, I., Zhang, W., Wasserman, D.H., Liew, C.W., Liu, J., Paik, J., DePinho, R.A., Stolz, D.B., Kahn, C.R., Schwartz, M.W., et al. (2015). FoxO1 integrates direct and indirect effects of insulin on hepatic glucose production and glucose utilization. Nat. Commun. *6*, http://dx.doi.org/10.1038/ncomms8079.

Obici, S., Feng, Z., Arduini, A., Conti, R., and Rossetti, L. (2003). Inhibition of hypothalamic carnitine palmitoyltransferase-1 decreases food intake and glucose production. Nat. Med. *9*, 756–761.

Owen, M.R., Doran, E., and Halestrap, A.P. (2000). Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. Biochem. J. *348*, 607–614.

Panjwani, N., Mulvihill, E.E., Longuet, C., Yusta, B., Campbell, J.E., Brown, T.J., Streutker, C., Holland, D., Cao, X., Baggio, L.L., and Drucker, D.J. (2013). GLP-1 receptor activation indirectly reduces hepatic lipid accumulation but does not attenuate development of atherosclerosis in diabetic male ApoE(-/-) mice. Endocrinology *154*, 127–139.

Park, S.J., Ahmad, F., Philp, A., Baar, K., Williams, T., Luo, H., Ke, H., Rehmann, H., Taussig, R., Brown, A.L., et al. (2012). Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cAMP phosphodiesterases. Cell *148*, 421–433.

Parker, H.E., Adriaenssens, A., Rogers, G., Richards, P., Koepsell, H., Reimann, F., and Gribble, F.M. (2012). Predominant role of active versus facilitative glucose transport for glucagon-like peptide-1 secretion. Diabetologia *55*, 2445–2455.

Patterson, L.M., Zheng, H., and Berthoud, H.R. (2002). Vagal afferents innervating the gastrointestinal tract and CCKA-receptor immunoreactivity. Anat. Rec. *266*, 10–20.

Patti, M.E., Houten, S.M., Bianco, A.C., Bernier, R., Larsen, P.R., Holst, J.J., Badman, M.K., Maratos-Flier, E., Mun, E.C., Pihlajamaki, J., et al. (2009). Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism. Obesity (Silver Spring) *17*, 1671–1677.

Perseghin, G., Regalia, E., Battezzati, A., Vergani, S., Pulvirenti, A., Terruzzi, I., Baratti, D., Bozzetti, F., Mazzaferro, V., and Luzi, L. (1997). Regulation of glucose homeostasis in humans with denervated livers. J. Clin. Invest. *100*, 931–941.

Peterli, R., Wölnerhanssen, B., Peters, T., Devaux, N., Kern, B., Christoffel-Courtin, C., Drewe, J., von Flüe, M., and Beglinger, C. (2009). Improvement in glucose metabolism after bariatric surgery: comparison of laparoscopic Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy: a prospective randomized trial. Ann. Surg. *250*, 234–241.

Plamboeck, A., Veedfald, S., Deacon, C.F., Hartmann, B., Wettergren, A., Svendsen, L.B., Meisner, S., Hovendal, C., Knop, F.K., Vilsbøll, T., and Holst, J.J. (2013a). Characterisation of oral and i.v. glucose handling in truncally vagotomised subjects with pyloroplasty. Eur. J. Endocrinol. *169*, 187–201.

Plamboeck, A., Veedfald, S., Deacon, C.F., Hartmann, B., Wettergren, A., Svendsen, L.B., Meisner, S., Hovendal, C., Vilsbøll, T., Knop, F.K., and Holst, J.J. (2013b). The effect of exogenous GLP-1 on food intake is lost in male truncally vagotomized subjects with pyloroplasty. Am. J. Physiol. Gastrointest. Liver Physiol. *304*, G1117–G1127.

Pocai, A., Obici, S., Schwartz, G.J., and Rossetti, L. (2005). A brain-liver circuit regulates glucose homeostasis. Cell Metab. *1*, 53–61.

Pressler, J.W., Haller, A., Sorrell, J., Wang, F., Seeley, R.J., Tso, P., and Sandoval, D.A. (2015). Vertical sleeve gastrectomy restores glucose homeostasis in apolipoprotein A-IV KO mice. Diabetes *64*, 498–507.

Price, N.L., Gomes, A.P., Ling, A.J., Duarte, F.V., Martin-Montalvo, A., North, B.J., Agarwal, B., Ye, L., Ramadori, G., Teodoro, J.S., et al. (2012). SIRT1 is required for AMPK activation and the beneficial effects of resveratrol on mitochondrial function. Cell Metab. *15*, 675–690.

Psichas, A., Reimann, F., and Gribble, F.M. (2015). Gut chemosensing mechanisms. J. Clin. Invest. *125*, 908–917.

Radtke, M.A., Nermoen, I., Kollind, M., Skeie, S., Sørheim, J.I., Svartberg, J., Hals, I., Moen, T., Dørflinger, G.H., and Grill, V. (2010). Six months of diazoxide treatment at bedtime in newly diagnosed subjects with type 1 diabetes does not influence parameters of beta-cell function and autoimmunity but improves glycemic control. Diabetes Care *33*, 589–594.

Rajala, M.W., Patterson, C.M., Opp, J.S., Foltin, S.K., Young, V.B., and Myers, M.G., Jr. (2014). Leptin acts independently of food intake to modulate gut microbial composition in male mice. Endocrinology *155*, 748–757.

Ramnanan, C.J., Edgerton, D.S., and Cherrington, A.D. (2012). Evidence against a physiologic role for acute changes in CNS insulin action in the rapid regulation of hepatic glucose production. Cell Metab. *15*, 656–664.

Rasmussen, B.A., Breen, D.M., Luo, P., Cheung, G.W., Yang, C.S., Sun, B., Kokorovic, A., Rong, W., and Lam, T.K. (2012). Duodenal activation of cAMP-dependent protein kinase induces vagal afferent firing and lowers glucose production in rats. Gastroenterology *142*, http://dx.doi.org/10.1053/j.gastro.2011.12.053.

Rasmussen, B.A., Breen, D.M., Duca, F.A., Côté, C.D., Zadeh-Tahmasebi, M., Filippi, B.M., and Lam, T.K. (2014). Jejunal leptin-PI3K signaling lowers glucose production. Cell Metab. *19*, 155–161.

Raybould, H.E., and Hölzer, H. (1992). Dual capsaicin-sensitive afferent pathways mediate inhibition of gastric emptying in rat induced by intestinal carbohydrate. Neurosci. Lett. *141*, 236–238.

Raybould, H.E., Gayton, R.J., and Dockray, G.J. (1988). Mechanisms of action of peripherally administered cholecystokinin octapeptide on brain stem neurons in the rat. J. Neurosci. *8*, 3018–3024.

Raybould, H.E., Meyer, J.H., Tabrizi, Y., Liddle, R.A., and Tso, P. (1998). Inhibition of gastric emptying in response to intestinal lipid is dependent on chylomicron formation. Am. J. Physiol. *274*, R1834–R1838.

Reimann, F., Habib, A.M., Tolhurst, G., Parker, H.E., Rogers, G.J., and Gribble, F.M. (2008). Glucose sensing in L cells: a primary cell study. Cell Metab. *8*, 532–539.

Richards, P., Parker, H.E., Adriaenssens, A.E., Hodgson, J.M., Cork, S.C., Trapp, S., Gribble, F.M., and Reimann, F. (2014). Identification and characterization of GLP-1 receptor-expressing cells using a new transgenic mouse model. Diabetes *63*, 1224–1233.

Ritter, R.C. (2011). A tale of two endings: modulation of satiation by NMDA receptors on or near central and peripheral vagal afferent terminals. Physiol. Behav. *105*, 94–99.

Rodieux, F., Giusti, V., D'Alessio, D.A., Suter, M., and Tappy, L. (2008). Effects of gastric bypass and gastric banding on glucose kinetics and gut hormone release. Obesity (Silver Spring) *16*, 298–305.

Rogers, R.C., and Hermann, G.E. (2008). Mechanisms of action of CCK to activate central vagal afferent terminals. Peptides *29*, 1716–1725.

Rubino, F. (2013). From bariatric to metabolic surgery: definition of a new discipline and implications for clinical practice. Curr. Atheroscler. Rep. *15*, 369.

Rubino, F., and Marescaux, J. (2004). Effect of duodenal-jejunal exclusion in a non-obese animal model of type 2 diabetes: a new perspective for an old disease. Ann. Surg. *239*, 1–11.

Rubino, F., Forgione, A., Cummings, D.E., Vix, M., Gnuli, D., Mingrone, G., Castagneto, M., and Marescaux, J. (2006). The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. Ann. Surg. *244*, 741–749.

Ryan, K.K., Tremaroli, V., Clemmensen, C., Kovatcheva-Datchary, P., Myronovych, A., Karns, R., Wilson-Pérez, H.E., Sandoval, D.A., Kohli, R., Bäckhed, F., and Seeley, R.J. (2014). FXR is a molecular target for the effects of vertical sleeve gastrectomy. Nature *509*, 183–188.

Salehi, M., Vahl, T.P., and D'Alessio, D.A. (2008). Regulation of islet hormone release and gastric emptying by endogenous glucagon-like peptide 1 after glucose ingestion. J. Clin. Endocrinol. Metab. *93*, 4909–4916.

Salehi, M., Prigeon, R.L., and D'Alessio, D.A. (2011). Gastric bypass surgery enhances glucagon-like peptide 1-stimulated postprandial insulin secretion in humans. Diabetes *60*, 2308–2314.

Salinari, S., le Roux, C.W., Bertuzzi, A., Rubino, F., and Mingrone, G. (2014). Duodenal-jejunal bypass and jejunectomy improve insulin sensitivity in Goto-Kakizaki diabetic rats without changes in incretins or insulin secretion. Diabetes *63*, 1069–1078.

Schauer, P.R., Burguera, B., Ikramuddin, S., Cottam, D., Gourash, W., Hamad, G., Eid, G.M., Mattar, S., Ramanathan, R., Barinas-Mitchel, E., et al. (2003). Effect of laparoscopic Roux-en Y gastric bypass on type 2 diabetes mellitus. Ann. Surg. *238*, 467–484.

Schauer, P.R., Kashyap, S.R., Wolski, K., Brethauer, S.A., Kirwan, J.P., Pothier, C.E., Thomas, S., Abood, B., Nissen, S.E., and Bhatt, D.L. (2012). Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N. Engl. J. Med. *366*, 1567–1576.

Schwartz, G.J. (2011). Gut fat sensing in the negative feedback control of energy balance—recent advances. Physiol. Behav. *104*, 621–623.

Schwartz, G.J., Fu, J., Astarita, G., Li, X., Gaetani, S., Campolongo, P., Cuomo, V., and Piomelli, D. (2008). The lipid messenger OEA links dietary fat intake to satiety. Cell Metab. *8*, 281–288.

Schwartz, M.W., Seeley, R.J., Tschöp, M.H., Woods, S.C., Morton, G.J., Myers, M.G., and D'Alessio, D. (2013). Cooperation between brain and islet in glucose homeostasis and diabetes. Nature *503*, 59–66.

Scott, W.R., and Batterham, R.L. (2011). Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy: understanding weight loss and improvements in type 2 diabetes after bariatric surgery. Am. J. Physiol. Regul. Integr. Comp. Physiol. *301*, R15–R27.

Scrocchi, L.A., Brown, T.J., MaClusky, N., Brubaker, P.L., Auerbach, A.B., Joyner, A.L., and Drucker, D.J. (1996). Glucose intolerance but normal satiety in mice with a null mutation in the glucagon-like peptide 1 receptor gene. Nat. Med. *2*, 1254–1258.

Seeley, R.J., Chambers, A.P., and Sandoval, D.A. (2015). The role of gut adaptation in the potent effects of multiple bariatric surgeries on obesity and diabetes. Cell Metab. *21*, 369–378.

Seghieri, M., Rebelos, E., Gastaldelli, A., Astiarraga, B.D., Casolaro, A., Barsotti, E., Pocai, A., Nauck, M., Muscelli, E., and Ferrannini, E. (2013). Direct effect of GLP-1 infusion on endogenous glucose production in humans. Diabetologia *56*, 156–161.

Shah, M., Law, J.H., Micheletto, F., Sathananthan, M., Dalla Man, C., Cobelli, C., Rizza, R.A., Camilleri, M., Zinsmeister, A.R., and Vella, A. (2014). Contribution of endogenous glucagon-like peptide 1 to glucose metabolism after Roux-en-Y gastric bypass. Diabetes *63*, 483–493.

Shin, N.R., Lee, J.C., Lee, H.Y., Kim, M.S., Whon, T.W., Lee, M.S., and Bae, J.W. (2014). An increase in the Akkermansia spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. Gut *63*, 727–735.

Sjöström, C.D., Lissner, L., Wedel, H., and Sjöström, L. (1999). Reduction in incidence of diabetes, hypertension and lipid disturbances after intentional weight loss induced by bariatric surgery: the SOS Intervention Study. Obes. Res. *7*, 477–484.

Speck, M., Cho, Y.M., Asadi, A., Rubino, F., and Kieffer, T.J. (2011). Duodenal-jejunal bypass protects GK rats from beta-cell loss and aggravation of hyperglycemia and increases enteroendocrine cells coexpressing GIP and GLP-1. Am. J. Physiol. Endocrinol. Metab. *300*, E923–E932.

Stefater, M.A., Perez-Tilve, D., Chambers, A.P., Wilson-Perez, H.E., Sandoval, D.A., Berger, J., Toure, M., Tschop, M., Woods, S.C., and Seeley, R.J. (2010). Sleeve gastrectomy induces loss of weight and fat mass in obese rats, but does not affect leptin sensitivity. Gastroenterology *138*, 2426–2436.

Stepensky, D., Friedman, M., Raz, I., and Hoffman, A. (2002). Pharmacokinetic-pharmacodynamic analysis of the glucose-lowering effect of metformin in diabetic rats reveals first-pass pharmacodynamic effect. Drug Metab. Dispos. *30*, 861–868.

Sundaresan, S., Shahid, R., Riehl, T.E., Chandra, R., Nassir, F., Stenson, W.F., Liddle, R.A., and Abumrad, N.A. (2013). CD36-dependent signaling mediates fatty acid-induced gut release of secretin and cholecystokinin. FASEB J. *27*, 1191–1202.

Takahashi, A., Tanaka, S., Miwa, Y., Yoshida, H., Ikegami, A., Niikawa, J., and Mitamura, K. (2000). Involvement of calmodulin and protein kinase C in cholecystokinin release by bombesin from STC-1 cells. Pancreas *21*, 231–239.

Tellez, L.A., Medina, S., Han, W., Ferreira, J.G., Licona-Limón, P., Ren, X., Lam, T.T., Schwartz, G.J., and de Araujo, I.E. (2013). A gut lipid messenger links excess dietary fat to dopamine deficiency. Science *341*, 800–802.

Thaler, J.P., and Cummings, D.E. (2009). Minireview: Hormonal and metabolic mechanisms of diabetes remission after gastrointestinal surgery. Endocrinology *150*, 2518–2525.

Timmers, S., Konings, E., Bilet, L., Houtkooper, R.H., van de Weijer, T., Goossens, G.H., Hoeks, J., van der Krieken, S., Ryu, D., Kersten, S., et al. (2011). Calorie restriction-like effects of 30 days of resveratrol supplementation on energy metabolism and metabolic profile in obese humans. Cell Metab. *14*, 612–622.

Titchenell, P.M., Chu, Q., Monks, B.R., and Birnbaum, M.J. (2015). Hepatic insulin signalling is dispensable for suppression of glucose output by insulin in vivo. Nature Commun. *6*, http://dx.doi.org/10.1038/ncomms8078.

Troy, S., Soty, M., Ribeiro, L., Laval, L., Migrenne, S., Fioramonti, X., Pillot, B., Fauveau, V., Aubert, R., Viollet, B., et al. (2008). Intestinal gluconeogenesis is a key factor for early metabolic changes after gastric bypass but not after gastric lap-band in mice. Cell Metab. *8*, 201–211.

Vahl, T.P., Tauchi, M., Durler, T.S., Elfers, E.E., Fernandes, T.M., Bitner, R.D., Ellis, K.S., Woods, S.C., Seeley, R.J., Herman, J.P., and D'Alessio, D.A. (2007). Glucagon-like peptide-1 (GLP-1) receptors expressed on nerve terminals in the portal vein mediate the effects of endogenous GLP-1 on glucose tolerance in rats. Endocrinology *148*, 4965–4973.

Vardarli, I., Arndt, E., Deacon, C.F., Holst, J.J., and Nauck, M.A. (2014). Effects of sitagliptin and metformin treatment on incretin hormone and insulin secretory responses to oral and "isoglycemic" intravenous glucose. Diabetes *63*, 663–674.

Vrieze, A., Van Nood, E., Holleman, F., Salojarvi, J., Kootte, R.S., Bartelsman, J.F., Dallinga-Thie, G.M., Ackermans, M.T., Serlie, M.J., Oozeer, R., et al. (2012). Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology *143*, http://dx.doi.org/10.1053/j.gastro.2012.06.031.

Waget, A., Cabou, C., Masseboeuf, M., Cattan, P., Armanet, M., Karaca, M., Castel, J., Garret, C., Payros, G., Maida, A., et al. (2011). Physiological and pharmacological mechanisms through which the DPP-4 inhibitor sitagliptin regulates glycemia in mice. Endocrinology *152*, 3018–3029.

Wang, Z., Wang, R.M., Owji, A.A., Smith, D.M., Ghatei, M.A., and Bloom, S.R. (1995). Glucagon-like peptide-1 is a physiological incretin in rat. J. Clin. Invest. *95*, 417–421.

Wang, P.Y., Caspi, L., Lam, C.K., Chari, M., Li, X., Light, P.E., Gutierrez-Juarez, R., Ang, M., Schwartz, G.J., and Lam, T.K. (2008). Upper intestinal lipids trigger a gut-brain-liver axis to regulate glucose production. Nature *452*, 1012–1016.

Whited, K.L., Lu, D., Tso, P., Kent Lloyd, K.C., and Raybould, H.E. (2005). Apolipoprotein A-IV is involved in detection of lipid in the rat intestine. J. Physiol. *569*, 949–958.

Williams, D.L., Baskin, D.G., and Schwartz, M.W. (2006). Leptin regulation of the anorexic response to glucagon-like peptide-1 receptor stimulation. Diabetes *55*, 3387–3393.

Wilson-Pérez, H.E., Chambers, A.P., Ryan, K.K., Li, B., Sandoval, D.A., Stoffers, D., Drucker, D.J., Pérez-Tilve, D., and Seeley, R.J. (2013). Vertical sleeve gastrectomy is effective in two genetic mouse models of glucagon-like Peptide 1 receptor deficiency. Diabetes *62*, 2380–2385.

Wittgrove, A.C., Clark, G.W., and Schubert, K.R. (1996). Laparoscopic Gastric Bypass, Roux-en-Y: Technique and Results in 75 Patients With 3-30 Months Follow-up. Obes. Surg. *6*, 500–504.

Wright, J., Campos, C., Herzog, T., Covasa, M., Czaja, K., and Ritter, R.C. (2011). Reduction of food intake by cholecystokinin requires activation of hindbrain NMDA-type glutamate receptors. Am. J. Physiol. Regul. Integr. Comp. Physiol. *301*, R448–R455.

Wu, V., Yang, M., McRoberts, J.A., Ren, J., Seensalu, R., Zeng, N., Dagrag, M., Birnbaumer, M., and Walsh, J.H. (1997). First intracellular loop of the human cholecystokinin-A receptor is essential for cyclic AMP signaling in transfected HEK-293 cells. J. Biol. Chem. *272*, 9037–9042.

Yamada, T., Kose, H., Ohta, T., and Matsumoto, K. (2012). Genetic dissection of complex genetic factor involved in NIDDM of OLETF rat. Exp. Diabetes Res. *2012*, 582546.

Yan, W., Polidori, D., Yieh, L., Di, J., Wu, X., Moreno, V., Li, L., Briscoe, C.P., Shankley, N., Dohm, G.L., and Pories, W.J. (2014). Effects of meal size on the release of GLP-1 and PYY after Roux-en-Y gastric bypass surgery in obese subjects with or without type 2 diabetes. Obes. Surg. *24*, 1969–1974.

Yang, C.S., Lam, C.K., Chari, M., Cheung, G.W., Kokorovic, A., Gao, S., Leclerc, I., Rutter, G.A., and Lam, T.K. (2010). Hypothalamic AMP-activated protein kinase regulates glucose production. Diabetes *59*, 2435–2443.

Zhang, H., DiBaise, J.K., Zuccolo, A., Kudrna, D., Braidotti, M., Yu, Y., Parameswaran, P., Crowell, M.D., Wing, R., Rittmann, B.E., et al. (2009). Human gut microbiota in obesity and after gastric bypass. Proc. Natl. Acad. Sci. USA *106*, 2365–2370.