Targeting the gastrointestinal tract to treat type 2 diabetes

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Abstract

The rising global rates of type 2 diabetes and obesity present a significant economic and social burden, underscoring the importance for effective and safe therapeutic options. The success of glucagon-like-peptide-1 receptor agonists in the treatment of type 2 diabetes, along with the potent glucose-lowering effects of bariatric surgery, highlight the gastrointestinal tract as a potential target for diabetes treatment. Furthermore, recent evidence suggests that the gut plays a prominent role in the ability of metformin to lower glucose levels. As such, the current review highlights some of the current and potential pathways in the gut that could be targeted to improve glucose homeostasis, such as changes in nutrient sensing, gut peptides, gut microbiota and bile acids. A better understanding of these pathways will lay the groundwork for novel gut-targeted antidiabetic therapies, some of which have already shown initial promise.

Key Words
- gut
- metformin
- gut sensing
- gut microbiota
- bile acids

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Introduction

The incidence of type 2 diabetes has more than doubled since 1980, with over 382 million affected individuals worldwide, in conjunction with an increase in obesity rates and the spread of a western lifestyle (Scully 2012). Given that type 2 diabetes has many comorbidities, such as hypertension, dyslipidaemia and cardiovascular disease, which contribute to the ever-rising economic burden, it is of utmost importance to develop successful therapeutic options. Chronic hyperglycaemia is a hallmark characteristic of type 2 diabetes and is, therefore, a main target for diabetes treatment. As such, metformin remains the most prescribed drug for type 2 diabetes due to its potent antihyperglycaemic effect, largely from a reduction in hepatic glucose production (Rojas & Gomes 2013). Although its mechanism of action still remains largely debated, recent evidence suggests a major role of the gastrointestinal tract in mediating metformin's glucose-lowering effect (Duca *et al*. 2015, Buse *et al*. 2016).

Interestingly, this is not the only evidence for a therapeutic role of the gut in diabetes treatment. Over the past decade, incretin-based therapies including glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-IV (DPP-IV) inhibitors have demonstrated powerful glucose-lowering efficacy, and are now commonly prescribed, usually in conjunction with metformin (Deacon & Lebovitz 2016, Madsbad 2016). Furthermore, despite being prescribed for the treatment of morbid obesity, metabolic/bariatric surgery results in rapid and sustained remission of diabetes, and is potentially more effective than conventional therapy (Mingrone *et al*. 2012, Mingrone *et al*. 2015).

The success of these treatments has expanded the classical view of the gastrointestinal (GI) tract from a 'digestion and absorption' organ to a major contributor to metabolic homeostasis. The GI tract exhibits crucial negative feedback signals, of both

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hormonal and neural origin, in response to incoming nutrients, preventing nutrient excess by suppressing food intake and endogenous nutrient production (Cote *et al*. 2014). The current review aims to highlight the current and potential therapeutic role of the GI tract in treating type 2 diabetes.

Gut peptide signalling in regulating glucose metabolism

Ingestion of nutrients leads to complex and integrative negative feedback mechanisms, which originate from the gut and contribute to the control of food intake, glucose metabolism, energy expenditure and thermogenesis, among other potential metabolic pathways (Bauer *et al*. 2016). In the case of glucose metabolism, postprandial gut-derived signals can lower hepatic glucose production, increase insulin production and secretion, reduce glucagon levels and alter glucose uptake. These signals are thought to originate from preasbsorptive nutrients being sensed on the apical surface of enteroendocrine cells (EECs) (Reimann *et al*. 2008), given the 'open-type' structure of these specialized epithelial endocrine cells. However, it is still unclear whether nutrient sensors of EECs are predominantly located on the apical side, with the possibility of basolateral nutrient sensing having been recently proposed (Christensen *et al*. 2015). Nonetheless, EECs can secrete gut peptides on their basolateral side in response to direct nutrient stimulation via binding to nutrient receptors localized on EECs, by intracellular metabolism and through neuroendocrine mechanisms (see Psichas *et al*. 2015*a* for extensive review). For example, fatty acids are potent secretogogues for both GLP-1 and CCK, potentially via activation of free fatty acid receptors (FFAR, FFAR1, FFAR4, activated by medium- to long-chain free fatty acids (Briscoe *et al*. 2003, Hirasawa *et al*. 2005), and FFAR2 and FFAR3, activated by short-chain fatty acids (Tolhurst *et al*. 2012, Psichas *et al*. 2015*b*)) localized on EECs, although the mechanisms of action appear to be more complex than originally thought. In the case of lipids, while *Ffar* knockout (KO) animals have severely impaired release of both GLP-1 (Edfalk *et al*. 2008) and CCK (Liou *et al*. 2011*b*) in response to a triglyceride challenge, it was recently demonstrated that LCFAs activate the FFAR1-G_q signalling pathway to induce only a modest release of GLP-1 (Hauge *et al*. 2015). However, both oleoylethanolamide and 2-monoacylglycerols, which are derived from triglycerides, activate a GPR119-G_s signalling cascade (Overton *et al*. 2006, Hansen *et al*. 2012*b*), leading to the hypothesis that triglyceride-induced gut peptide signalling is likely due to a combined effect of direct LCFA-FFAR1-G_q signalling and activation of the G_s signalling pathway in EECs (Hauge *et al*. 2015). In addition to a direct action on FFARs, fatty acids are also taken up by the intestine, and mice lacking absorptive proteins such as CD36 or FAT4 results in impaired gut peptide release (Poreba *et al*. 2012, Sundaresan *et al*. 2013). This may be due to intracellular metabolism and activation of PKC-ζ or PKC-δ to induce GLP-1 or CCK release, respectively (Iakoubov *et al*. 2007, Breen *et al*. 2011), or via alteration of cellular respiration and stimulation of glycolysis (Clara *et al*. 2016). The same complexity in nutrient-induced gut peptide stimulation is observed for carbohydrates. For example, carbohydrates can be sensed by the T1R2/T1R3 sweet taste receptor found in the gut (Jang *et al*. 2007), although the physiological relevance of sweet taste receptor activation on gut peptide signalling in humans remains debated (Parker *et al*. 2009). Conversely, recent work suggests that GLP-1 release occurs via uptake of glucose coupled with Na^+ through the sodium/glucose cotransporter member 1 (SGLT1), inducing small currents triggered by increased Na^+ which leads to membrane depolarization and voltage-gated Ca2+ entry, ultimately resulting in GLP-1 secretion (Gribble *et al*. 2003, Kuhre *et al*. 2015). Less is known about intestinal protein sensing, with GPR93, CaSR and PepT1 all being suggested to mediate protein-induced gut peptide release (Nemoz-Gaillard *et al*. 1998, Darcel *et al*. 2005, Liou *et al*. 2011*a*,*c*).

In the traditional view, the proximal intestine contains I-cells, which secrete CCK, and GIP-releasing K-cells, while L-cells cosecrete PYY and GLP-1 and are located mainly in the distal intestine (Little *et al*. 2006). However, recent work has challenged these classical views, as individual enteroendocrine cells have been shown to express a variety of gut peptides (Egerod *et al*. 2012, Habib *et al*. 2012, Svendsen *et al*. 2015, Grunddal *et al*. 2016), while the proximal small intestine has been shown to secrete significant amounts of GLP-1 (Theodorakis *et al*. 2006). Once released, gut peptides can act locally on afferent neurons innervating the GI tract that signal to the caudal brainstem or enteric neurons, and/or they can enter the circulation to act centrally, or on peripheral targets, to regulate glucose metabolism (Cote *et al*. 2014). For example, GLP-1 receptors (GLP-1Rs) are located on vagal afferents that innervate the gut in close proximity to L-cells (Richards *et al*. 2014), indicating a possible paracrine gut–brain axis for mediating its glycaemic effects. However, GLP-1Rs are also located on neurons innervating the portal vein (Vahl *et al*. 2007), on β cells of the pancreas (Pyke *et al*. 2014), and in the central

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nervous system (Shimizu *et al*. 1987, Heppner *et al*. 2015), all possible targets for GLP-1 action (described in more detail below). Nonetheless, most studies demonstrate that vagal neural transmission is necessary for nutrient-induced gut feedback as anaesthetics, neurotoxins or vagotomy abolishes nutrient-induced reductions in food intake (Schwartz 2011), and in the case of lipid-induced CCK release, the lowering of hepatic glucose production (Wang *et al*. 2008*a*).

In response to lipids, CCK is released from EECs in a process dependent on intracellular esterification of long-chain fatty acids to long-chain fatty acyl-CoA via acyl-CoA synthase-3 (Sundaresan *et al*. 2013) and upon PKC-δ stimulation (Breen *et al*. 2011, Kokorovic *et al*. 2011). Released CCK activates the CCK receptor (CCK1-R) on vagal afferents innervating the small intestine (Raybould *et al*. 1988), which leads to PKA activation and vagal afferent firing (Rasmussen *et al*. 2012). Vagal afferent activation enhances N-Methyl-D-aspartate (NMDA) receptor-mediated neuronal transmission in the nucleus of the solitary tract (NTS) to lower glucose production via the hepatic vagal branch (Rasmussen *et al*. 2012). Interestingly, the ability of intestinal lipids and CCK to reduce glucose production is diminished in rats fed a 3-day high-fat diet (Wang *et al*. 2008*a*, Cheung *et al*. 2009), highlighting the pathophysiological relevance of this pathway. Although preliminary studies demonstrate that preabsorptive lipids may not potently inhibit hepatic glucose production in humans (Xiao *et al*. 2015), this lipid-CCK pathway requires much more extensive and thorough testing. Furthermore, 8 weeks of treatment with the bile acid sequestrant, colesevelam, improves glycaemic control in humans with impaired glucose tolerance through a mechanism dependent on prevention of bile acid absorption and increased local CCK secretion (Marina *et al*. 2012), suggesting this aforementioned CCK gut–brain–liver axis could be of therapeutic relevance. Additionally, cotreatment of a CCK receptor agonist with a GLP-1R agonist has demonstrated initial therapeutic promise (Irwin *et al*. 2015; see section below).

GLP-1 has been widely studied for its incretin effect, where it stimulates an increase in insulin secretion at the level of the pancreas (Kreymann *et al*. 1987, Mojsov *et al*. 1987). Interestingly, recent evidence suggests that GLP-1 may additionally exert its effect via activation of visceral afferent neurons (Yamamoto *et al*. 2003), challenging the conventional model of GLP-1 action. GLP-1 is rapidly degraded by dipeptidyl peptidase-IV (DPP-IV) in the portal vein and liver, leaving only 10–15% of secreted GLP-1 for entry into the systemic circulation (Holst & Deacon 2005). As a result, studies hypothesize that effects on insulin release, as well as other glucoregulatory effects of GLP-1, such as decreased glucose production, increased glucose utilization and regulation of counter-regulatory hormones, are mediated at least in part by a gut–brain–periphery axis (Burcelin *et al*. 2001). Complicating this model further, GLP-1 can also act centrally to regulate food intake (Tang-Christensen *et al*. 1996), energy expenditure (Lockie *et al*. 2012), GI function (Seeley *et al*. 2000) and importantly, glucose homeostasis (Knauf *et al*. 2005, Gustavson *et al*. 2008). However, in contrast to these studies, others suggest that the glucoregulatory effects of GLP-1 are primarily mediated by pancreatic GLP-1R activation (Lamont *et al*. 2012, Smith *et al*. 2014). Nonetheless, GLP-1 plays an important role in the regulation of metabolism and glucose homeostasis, and as a result, some of the latest drugs to come onto the market have aimed to exploit the GLP-1R signalling pathway. Two main drug classes have emerged, degradation-resistant GLP-1R agonists and DPP-IV inhibitors.

Incretin-based drug

GLP-1R agonists

GLP-1R agonists commonly fall into two categories based on their duration of receptor activation: short-acting compounds, which deliver short-lived GLP-1R activation, and long-acting compounds, which activate their receptor continuously at their recommended dose (Madsbad 2016). Short-acting compounds include exenatide (Byetta), which was the first GLP-1R agonist approved for clinical use, and lixisenatide (Lyxumia), which has subsequently been approved for use in Europe, but not in the USA. Exenatide exhibits approximately 50% amino acid identity with human GLP-1 and has an affinity for the GLP-1R that is equivalent to native GLP-1. It contains a glycine residue at position 2, which provides resistance to degradation by DPP-IV and an increased circulating half-life (Furman 2012). Exenatide is the most widely studied of the GLP-1R agonists, with over 7 years of continuous clinical follow-up data. Early clinical trials examining the efficacy of exenatide showed that twice-daily 10 μg injections effectively lowered both fasting and postprandial glucose concentrations in diabetic individuals after 30 weeks of treatment (Buse *et al*. 2004, DeFronzo *et al*. 2005, Kendall *et al*. 2005).

The success of exenatide led to the development of new long-acting GLP-1R agonists with pharmacokinetic properties designed for once-daily or once-weekly

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administration. Liraglutide (marketed as Victoza) is a modified form of GLP-1 that contains a Ser34Arg substitution and has a C16 palmitoyl fatty acid side chain at Lys26, which allow binding to serum albumin and provide resistance to DPP-IV degradation (Lovshin & Drucker 2009). Liraglutide thus exhibits a prolonged half-life with stable plasma levels for up to 13 h after subcutaneous injection. Liraglutide administration (1.8 mg once daily) results in 24-h glucose control when prescribed as monotherapy or in combination therapy with oral glucose-lowering agents (Buse *et al*. 2009, Garber *et al*. 2009, Marre *et al*. 2009, Nauck *et al*. 2009, Russell-Jones *et al*. 2009). Other long-acting GLP-1R agonists include the once-weekly formulations of exenatide (Bydureon), albiglutide (Eperzan and Tanzeum) and dulaglutide (Trulicity) (Madsbad 2016). Differences in the duration of action largely account for differences in glucose control between GLP-1R agonists. For example, delayed gastric emptying is more strongly associated with short-acting GLP-1R agonists, resulting in greater effects on postprandial plasma glucose when compared with long-acting agonists (Drucker *et al*. 2008, Ji *et al*. 2013, Kapitza *et al*. 2013, Meier *et al*. 2015). On the other hand, the longer half-lives of long-acting GLP-1R agonists allow a greater improvement in 24-h glucose control, including fasting plasma glucose, when compared with short-acting agonists (Drucker *et al*. 2008, Buse *et al*. 2009, Blevins *et al*. 2011, Kapitza *et al*. 2013).

Despite the popularity of GLP-1R agonists, considerable mystery surrounds the main site of action for GLP-1R agonist antidiabetic effects. Exenatide readily crosses the blood–brain barrier, even more efficiently than native GLP-1 (Kastin & Akerstrom 2003), and it has been shown to activate brain regions involved in food reward and glucose homeostasis when administered subcutaneously (Daniele *et al*. 2015). The effects of exenatide on food intake may be mediated by its central action, as exenatide-induced reductions in energy intake in humans have been associated with increased hypothalamic connectivity (Schlogl *et al*. 2013), and intracerebroventricular injection of the GLP-1R antagonist, exendin-9, blocks the inhibitory effects of exenatide on energy intake in rodents (Kanoski *et al*. 2011). However, the effects of exenatide on glucose regulation do not appear to be dependent on central GLP-1R activation (Lamont *et al*. 2012), and evidence suggests that exenatide may exert its effects on glycaemia through direct action on the pancreas (Smith *et al*. 2014). There has also been evidence that the anorexic effects of exenatide are mediated, at least in part, by the activation of GLP-1R expressed on peripheral vagal afferents. However, studies suggest that although the early effects of exenatide require vagal afferent signalling, the later effects do not (Kanoski *et al*. 2011, Labouesse *et al*. 2012). Similar to exenatide, the main site of action of liraglutide remains unknown. Interestingly, liraglutide has been shown to improve insulin sensitivity in humans, as assessed by the hyperinsulinaemic euglycaemic clamp (Jinnouchi *et al*. 2015), indicating that in addition to its effects on insulin secretion, liraglutide also exhibits beneficial extrapancreatic effects on glycaemia. Liraglutide also passes the blood–brain barrier and it has been shown to bind to neurons within the arcuate nucleus and other sites within the hypothalamus (Secher *et al*. 2014). Evidence suggests that the anorectic effects of liraglutide are mediated via GLP-1Rs expressed both centrally and on vagal afferent neurons (Kanoski *et al*. 2011, Secher *et al*. 2014). However, whether liraglutide mediates its glucose-lowering effects through a manner similar to its anorectic effects requires attention. Some studies suggest that liraglutide-induced improvements in glucose tolerance do not require central or vagal GLP-1R (Sisley *et al*. 2014) and that its effects on glycaemia are via direct action on the pancreas (Smith *et al*. 2014). Thus, although the effects of liraglutide on glycaemia appear to be primarily dependent on the activation of pancreatic GLP-1R, central and vagal GLP-1R signalling should not be overlooked given their importance in lowering food intake and body weight, which is a primary treatment strategy for type 2 diabetes. A better understanding of the exact mechanisms for the glucose-lowering effects of GLP-1R agonists could result in more targeted drug designs to exploit the specific pathways.

DPP-IV inhibitors

DPP-IV inhibitors, also referred to as 'incretin enhancers', lower blood glucose levels through a prolongation of the action of GLP-1, and to a lower extent, GIP (a second incretin hormone produced in the small intestine) (Hansotia *et al*. 2004). Typically, DPP-IV inhibitors reduce DPP-IV activity by about 80%, which corresponds to a twofold increase in biologically active GLP-1 (Heine *et al*. 2005). This is associated with an increase in insulin and decrease in glucagon secretion and reduced fasting and postprandial glucose levels in individuals with diabetes (Heine *et al*. 2005).

Sitagliptin was the first DPP-IV inhibitor approved for use in 2006. It is a nonpeptide heterocyclic compound with rapid onset and a long duration of action, which

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facilitates once-daily dosing (Lovshin & Drucker 2009). Vildagliptin and saxagliptin were approved for use soon after sitagliptin; these compounds are cyanopyrrolidines with a slow onset and prolonged action upon binding to DPP-IV (Lovshin & Drucker 2009). The shorter half-life of vildagliptin requires twice-daily dosing (Lovshin & Drucker 2009). However, saxagliptin is suitable for once-daily dosing as a result of the presence of the active metabolite BMS-510849, which also inhibits DPP-IV (Trujillo & Nuffer 2014). The most recent DPP-IV inhibitors to reach the market are linagliptin (a methylxanthine) and alogliptin (a heterocyclic aminopiperidine), which are also administered once daily due to their relatively longer half-lives (Trujillo & Nuffer 2014, Handelsman *et al*. 2015). Each DPP-IV inhibitor elevates GLP-1 and improves glycaemia to a similar degree (Trujillo & Nuffer 2014, Handelsman *et al*. 2015). Once DPP-IV is maximally inhibited, glycated haemoglobin (HbA1c) reductions plateau; therefore, improvements are consistent across this drug class and there is no basis for differentiation regarding efficacy (Lovshin & Drucker 2009).

Despite the success of DPP-IV inhibitors, the cellular site that is responsible for their glucoregulatory effects has yet to be determined. Indeed, it is likely that increased endogenous GLP-1 could reach the pancreas and brain to exert the aforementioned effects. Studies in rodents indicate that a dose of sitagliptin that is sufficient to inhibit intestinal, but not systemic, DPP-IV activity is sufficient for improving glucose tolerance and insulin levels. This effect is associated with increased activity of the vagal nerve, suggesting that DPP-IV inhibitors may regulate glycaemia predominantly through local inhibition of intestinal DPP-IV activity and activation of neuronal GLP-1Rs (Waget *et al*. 2011).

Cocktail therapy

Despite the early beneficial effects of gut peptide-based therapies, the signalling pathways involved are redundant and the body can adjust. Therefore, it follows that the design of multitarget peptides capable of modulating more than one hormonal pathway could have distinct therapeutic benefits for the treatment of type 2 diabetes. Combination therapy with long-acting GIP and GLP-1 mimetics has been considered in preclinical studies with some success (Irwin & Flatt 2009); however, issues of separate drug formulation and dosing limits the therapeutic success. As such, a single hybrid peptide, MAR701, has been developed that can directly activate both GIP receptor and GLP-1R and appears to have beneficial effects in rodents (Finan *et al*. 2013). Further studies have investigated the effects of GLP-1R agonism combined with either glucagon receptor agonism (Pan *et al*. 2006, Day *et al*. 2009, 2012) or antagonism (Pocai *et al*. 2009). Although contradictory in nature, these contrasting regimens utilize both the beneficial glucose-lowering effects of GLP-1, combined with either inhibition of glucagon-mediated gluconeogenesis and glycogenolysis (Sinclair & Drucker 2005), and activation of glucagon pathways involved in energy turnover and weight loss (Pocai *et al*. 2009). Another modified hybrid peptide, ZP3022, involves a combined GLP-1-gastrin agonist (Fosgerau *et al*. 2013), which activates GLP-1R and CCK2-R and improves glycaemic control in db/db mice through enhancement of β cell mass (Fosgerau *et al*. 2013). Perhaps a more appealing peptide would be one that targets the GLP-1R and CCK1-R given the involvement of the CCK1-R in the activation of the gut–brain–liver axis. Indeed, combined administration of long-acting GLP-1R and CCK1-R agonists has shown pronounced synergistic metabolic benefits in rodent models of type 2 diabetes, including improved glycaemic control and loss of body weight (Irwin *et al*. 2013, Trevaskis *et al*. 2015). As such, a novel CCK/GLP-1 hybrid peptide based on the chemical structures of the CCK1-R agonist, (pGlu-Gln)-CCK-8, and exenatide has recently been described and shown to have significant therapeutic potential in high-fat-fed mice (Irwin *et al*. 2015). This molecule clearly warrants further study as a potential new treatment option for type 2 diabetes.

Considering the evident therapeutic efficacy of dual target peptide therapies, single compounds with the ability to activate three or more regulatory peptides could potentially provide even greater metabolic benefits. As a result, modified peptides with the ability to activate glucagon, GLP-1 and GIP receptors have been developed and have been shown to produce dramatic improvements in glucose homeostasis and overall metabolic control in high-fat-fed mice (Bhat *et al*. 2013*a*,*b*, Finan *et al*. 2015). Despite the clear potential of these tri-agonists, issues regarding the ratio of GIP, GLP-1 and glucagon receptor activation still requires investigation. As such, a recent study has reported the distinct beneficial effects of a balanced glucagon, GLP-1 and GIP receptor tri-agonist for the correction of obesity and diabetes in high-fat-fed mice (Finan *et al*. 2015). There is, therefore, a clear and attractive rationale for further testing of multitarget peptides for the treatment of type 2 diabetes in humans. In addition, given the recent findings that EECs coexpress a variety of gut peptides (Egerod *et al*. 2012, Habib *et al*. 2012, Svendsen *et al*. 2015, Grunddal *et al*. 2016), it may be

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possible to develop a drug that promotes the cosecretion of multiple gut peptides from EECs. For example, infusion of bombesin, the phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine, or peptone stimulates the cosecretion of GLP-1, PYY, neurotensin and CCK (Svendsen *et al*. 2015), and interestingly, neurotensin acts synergistically with GLP-1 to regulate metabolism (Grunddal *et al*. 2016). This suggests that stimulating the release of an endogenous gut peptide 'cocktail', similar to engineering poly-agonists that mimic these peptides (Day *et al*. 2009, 2012, Finan *et al*. 2013, 2015), could be a useful alternative approach for improving metabolic control in type 2 diabetes.

The potential treatment of diabetes via mimicry of gut peptide signalling is bolstered by the success of bariatric surgery. Indeed, bariatric surgery has demonstrated great efficacy in normalizing blood glucose levels and ameliorating diabetes in obese populations, which has been suggested to be due in part to improvements in intestinal nutrient sensing and subsequent modulation of the secretion and biological action of numerous gut-derived peptides (see below). The following section aims to not only describe the various surgical procedures demonstrated to improve glucose regulation, but to introduce some of the major hypothesized mechanisms, in addition to intestinal nutrient sensing, underlying the success of bariatric surgery and to highlight the current therapeutic strategies directly targeting these mechanisms.

Bariatric surgery

The long-term success of bariatric surgery to reverse diabetes in obese patients underscores the need for identifying the mechanisms of action. Bariatric surgery encompasses many surgical procedures that are either restrictive in nature, by altering the stomach size or nutrient flux into the stomach, or involve the rerouting of the intestinal tract (Fig. 1). Roux-en-y gastric bypass surgery (RYGB) is one of the most commonly performed bariatric surgical procedures and involves a reduction in the size of the stomach, by creating a gastric pouch out of the upper portion of the stomach, and rerouting the intestinal tract by connecting the proximal jejunum to the stomach and thus excluding the duodenum (Ward & Prachand 2009). RYGB induces substantial effects on diabetes remission (Buchwald *et al*. 2004) and produces metabolic benefits that are maintained for over 10 years (Karlsson *et al*. 2007). However, the biliopancreatic diversion with duodenal switch (BPD-DS) procedure, which involves a pylorus-preserving vertical sleeve gastrectomy (VSG) (as opposed to the original BPD procedure, which involved a distal gastrectomy sacrificing the pylorus (Scopinaro *et al*. 1979)) and creation of a Roux limb, a long biliopancreatic limb and a short common channel, achieves diabetes resolution rates that are significantly better than RYGB (90% vs 70%) (Buchwald *et al*. 2004, 2009). However, despite its long-term metabolic success (Buchwald *et al*. 2004, 2009), the technical difficulty and meticulous patient surveillance have limited the use of this surgical technique to about 17% of all bariatric surgeries (Buchwald *et al*. 2009), although it is the metabolic surgery of choice for some surgeons (Marceau *et al*. 2015). Interestingly, VSG alone has substantial weight loss effects and appears to induce rapid and long-term diabetes resolution in obese type 2 diabetics (Bayham *et al*. 2012, Madsbad *et al*. 2014), which has been attributed to much more than simply restriction (see below or Seeley *et al*. 2015 for review).

To evaluate the relative contribution of gastric restriction vs rearrangement of the intestinal tract to the antidiabetic effects of bariatric surgery, an experimental procedure entitled duodenal-jejunal bypass (DJB) was developed. This procedure involves repositioning the intestinal tract without restriction or exclusion of the stomach. Although DJB does not elicit the same weight loss effects as RYGB or BPD, this procedure has been shown to produce glucose-lowering effects in nonobese rodents (Rubino *et al*. 2004), and in a small subset of nonobese or mild-obese humans with type 2 diabetes, independent of weight loss (Cohen *et al*. 2007, 2012, Lee *et al*. 2010, Geloneze *et al*. 2012). Moreover, in Asia, a novel surgery similar to a BPD-DS has been developed that involves a DJB with VSG, and has demonstrated initial success in the treatment of diabetes (Kasama *et al*. 2009, Lee *et al*. 2014). Lastly, another experimental metabolic surgery still in early human trials is ileal interposition (with or without VSG), which involves resection of 10–20 cm of the distal ileum and its transposition into the proximal jejunum. This procedure results in weight loss, reduced food intake and improved glycaemic regulation in both rodents and humans (Wang *et al*. 2008*b*, Gagner 2011, Zhang *et al*. 2011, Grueneberger *et al*. 2013, Grueneberger *et al*. 2014, Ramzy *et al*. 2014).

Surgical intervention remains one of the most successful treatment options for the remission of diabetes. However, it is important that the best metabolic procedure is selected with benefits vs risks assessed for

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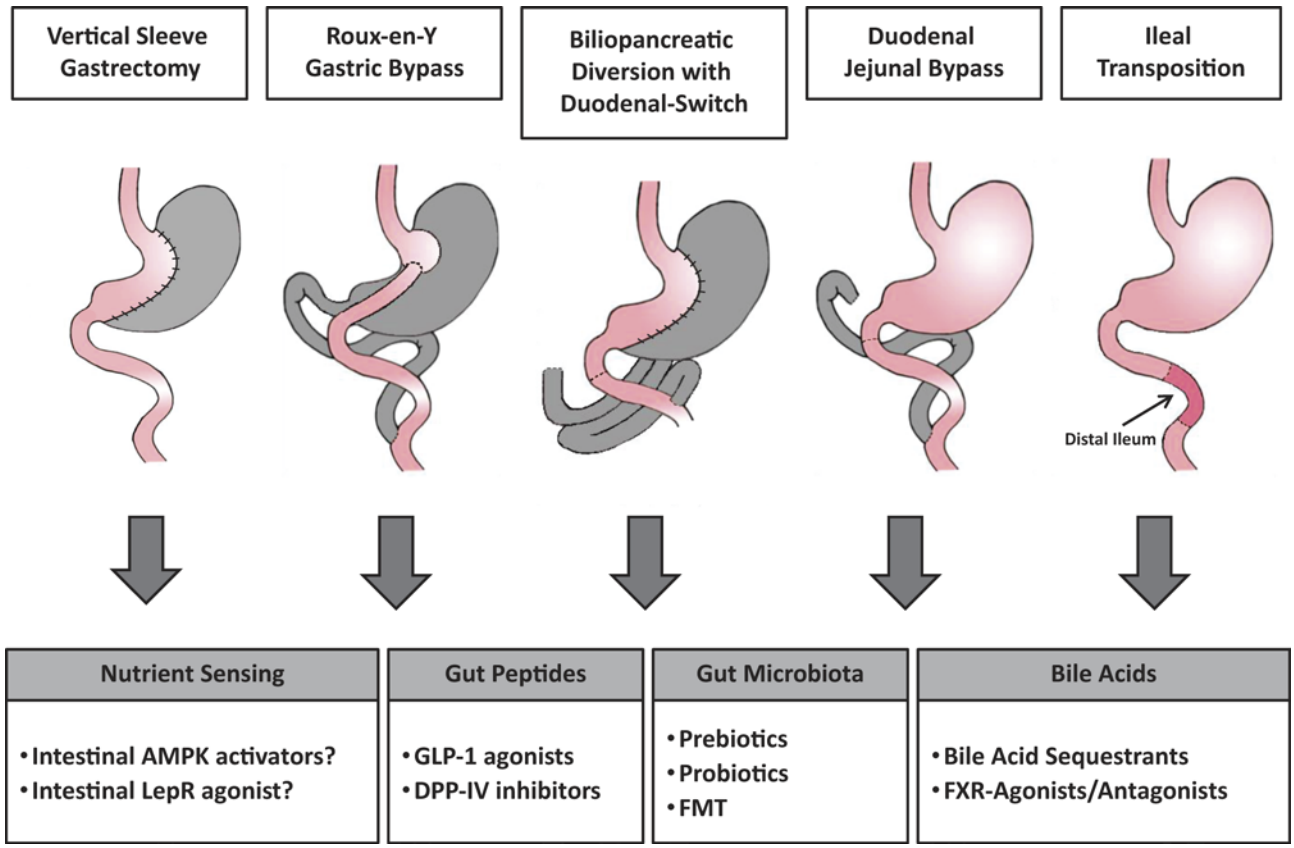

Figure 1
Effectiveness of bariatric surgery yields possible 'gut-centered' treatment options for type 2 diabetes. Bariatric surgery, in the form of vertical sleeve gastrectomy, roux-en-Y gastric bypass, biliopancreatic diversion with duodenal switch, duodenal-jejunal bypass or ileal transposition, have all been demonstrated to exert beneficial effects on glucose homeostasis, hypothesized to be due to changes in nutrient sensing, gut peptide signalling, gut microbiota and/or bile acids. Current gastrointestinal-based therapeutic options for type 2 diabetes involve drugs or treatments targeting these pathways.

each individual patient (Castagneto Gissey *et al*. 2016). Despite the relative risks associated with procedures like RYGB and BPD-DS, a better understanding of these surgeries may continue to lead to less invasive and risky surgical procedures that equal in effectiveness. Moreover, noninvasive devices mimicking bariatric surgery could provide substantial benefits, such as the duodenal endoluminal sleeve, which involves inserting a flexible tube that inhibits the interaction of nutrients with the duodenum and has been shown to improve glucose regulation (Habegger *et al*. 2014). Ultimately, elucidation of the mechanisms underpinning the resolution of diabetes following bariatric surgery could lead to the discovery of novel pharmacological bariatric mimetics that could one day replace the need for bariatric surgery altogether. Therefore, the following sections describe some of the more developed hypotheses regarding the success of bariatric surgery, mainly the role of intestinal gut peptide signalling, gut microbiota and bile acids, and highlight the therapeutic potential of directly targeting these pathways.

Gut peptide and nutrient sensing

Given that many patients have exhibited postsurgical changes in gut hormone secretion (Rodieux *et al*. 2008), many studies have investigated whether changes in nutrient sensing mediate the weight loss and glucose-lowering effects of this procedure. One of the leading candidates for the success of bariatric surgery is altered gut peptide signalling, mainly GLP-1 (Salehi *et al*. 2011, Jimenez *et al*. 2013). Indeed, after RYGB, there is an increase in the number of gut peptide-expressing EECs (Mumphrey *et al*. 2013) and consequently, increased postprandial gut peptide secretion (Madsbad *et al*. 2014). In the case of GLP-1, many studies have shown an increase in circulating GLP-1 levels following RYGB and VSG (Rodieux *et al*. 2008, Chambers *et al*. 2011,

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Salehi *et al*. 2011, Jimenez *et al*. 2013), and postprandial GLP-1 levels are increased as early as 2 days postsurgery (le Roux *et al*. 2007) and have persisted as long as 10 years postsurgery (Dar *et al*. 2012). Improvements in glucose tolerance following RYGB or VSG in rats are abolished with exendin-9 administration (Chambers *et al*. 2011), all suggesting a role for GLP-1 in the glucose-lowering success of RYGB. Some studies argue against this (Clements *et al*. 2004, Rubino *et al*. 2004, le Roux *et al*. 2007), whereas some have shown that GLP-1 levels do not rise accordingly (Salinari *et al*. 2014), inhibition of GLP-1 signalling has no effect on glycaemia following RYGB (Jimenez *et al*. 2013, Shah *et al*. 2014) and GLP-1R deficient mice still exhibit improved glycaemia following RYGB and VSG (Wilson-Perez *et al*. 2013, Mokadem *et al*. 2014). As such, other gut peptides have been implicated as potential contributors to improved glycaemia following bariatric surgery.

Plasma PYY levels are increased following RYGB (le Roux *et al*. 2006, 2007, Rodieux *et al*. 2008) and DJB (Zhang *et al*. 2011, Liu *et al*. 2012, Imoto *et al*. 2014), and a causal link between PYY signalling and weight loss has been suggested for both humans (le Roux *et al*. 2007, Morinigo *et al*. 2008) and rodents (Chandarana *et al*. 2011), although studies investigating the role of PYY in the antidiabetic effects of these bariatric procedures are lacking. Interestingly, PYY action has been correlated with increased sensitivity to GLP-1 and improved glucose tolerance following bariatric surgery (Chandarana *et al*. 2013), suggesting that studies investigating the role of PYY in the glucoregulatory effects of bariatric surgery are warranted. Another gut peptide identified as a possible mediator of the beneficial effects of bariatric surgery is ghrelin. Plasma ghrelin levels are substantially reduced following VSG (Chambers *et al*. 2013); however, VSG is equally effective in improving glucose tolerance and lowering food intake and body weight in ghrelin-deficient and wild-type mice (Chambers *et al*. 2013), indicating that the beneficial effects of VSG are not dependent on reduced ghrelin signalling. Other factors have been shown to be altered following one or more of these procedures such as CCK, GIP and glucagon (Jacobsen *et al*. 2012, Rhee *et al*. 2015). Therefore, improvements in glycaemia following bariatric surgery may not be dependent on changes in the action of a single gut peptide, and it is very possible that an adaptive shift increases postingestive feedback, contributing to the rapid lowering of glucose levels.

Given that the rearrangement of the intestinal tract results in an increased flux of nutrients into the jejunum, it was hypothesized that increased jejunal nutrient sensing could mediate the improvements in glucose regulation. Indeed, intrajejunal nutrients lower hepatic glucose production via a gut–brain–liver neuronal axis, independent of changes in circulating insulin levels, while inhibition of these jejunal nutrient sensing pathways altered the rapid glucose-lowering effect of DJB in streptozotocin (STZ)-induced uncontrolled diabetic rats during refeeding (Breen *et al*. 2012). While lowering of glucose in STZ-induced uncontrolled diabetic rats following DJB was associated with increased circulating GLP-1 levels, this was not the case following DJB in BBdp rats (Breen *et al*. 2012), Zucker diabetic fatty rats (Patel *et al*. 2014) or Goto-Kakizaki rats (Salinari *et al*. 2014), further arguing against the importance of GLP-1 in DJB. Interestingly, in a follow-up study, it was shown that direct leptin infusion into the jejunum activates jejunal leptin receptor-phosphoinositide-3-kinase signalling to lower endogenous glucose production through a neuronal network, while blocking jejunal leptin receptor signalling abolished the improvements in glucose homeostasis of DJB-diabetic rodents during refeeding (Rasmussen *et al*. 2014). However, it is important to note that for these studies, the testing period was only 2 weeks following DJB, and while this demonstrates that the rapid remission of diabetes following GBP may be due in part to nutrient- and hormonal-jejunal sensing mechanisms, the long-term potential of these sensing mechanisms remains unknown. The cell-type mediating the effect of jejunal leptin following DJB has not been characterized, the nodose ganglia contains leptin receptors (Li *et al*. 2011*b*) and studies suggest that leptin receptors on vagal afferents, rather than intestinal epithelial cells, play a role in the development of obesity and hyperglycaemia (de Lartigue *et al*. 2014). Thus, it is likely that leptin is acting on vagal afferents innervating the gut to regulate glucose homeostasis. However, whether this pathway can be exploited to treat hyperglycaemia remains to be explored. Interestingly, while leptin treatment in obesity is generally unsuccessful due to leptin resistance, cotreatment of leptin with peptides that promote weight loss and leptin sensitivity, such as amylin and CCK, has been shown to be effective in improving glucose homeostasis in rodents (Sadry & Drucker 2013, Trevaskis *et al*. 2015). Furthermore, human analogues of amylin and leptin were successful in lowering body weight in clinical trials (Ravussin *et al*. 2009); however, safety concerns lead to the discontinuation of development. Nonetheless, future studies investigating not just leptin receptor activation, but rather vagal signalling in general, may hold promise for the development of novel antidiabetic therapies.

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Bile acids

In addition to distal intestinal nutrient sensing and gut peptide changes, rearranging the intestinal tract during bariatric surgery profoundly alters bile acid levels and composition, which has been suggested as key contributor to its success (Seeley *et al*. 2015). Bile acids have been implicated in the regulation of glucose homeostasis through their effects on glucose production and glucose-induced insulin secretion (Thomas *et al*. 2008, 2009). Beyond acting as detergent for luminal fat digestion and absorption, bile acids act as endocrine factors, activating the G protein-coupled receptor TGR5, and a ligand-activated transcription factor farnesoid X receptor (FXR) (Fiorucci *et al*. 2009). In RYGB, bile acids flow undiluted through the biliopancreatic limb and do not mix with food until reaching the common channel of the distal jejunum. As such, increased presence of bile acids in this region could activate TGR5, which is localized on EECs, and can stimulate the release of gut peptides such as GLP-1 and PYY (Katsuma *et al*. 2005, Pournaras *et al*. 2012). However, increased gut peptide levels following RYGB have been shown to be independent of changes in bile acids (Bhutta *et al*. 2014, Jorgensen *et al*. 2015), and recent evidence shows that increased GLP-1 levels following VSG do not require TGR5 signalling, although TGR5 was shown to contribute to the glucoregulatory benefits of VSG in this study (McGavigan *et al*. 2015). Interestingly, the effects of VSG on body weight and glucose levels were abolished in *Fxr* knockout mice, suggesting a role for FXR in the metabolic effects of this procedure (Ryan *et al*. 2014). Indeed, FXR is essential for normal glucose homeostasis (Ma *et al*. 2006), and bile acid activation of FXR induces FGF19 (in humans and its mouse orthologue FGF15) release from the ileal intestinal epithelium (Zhang *et al*. 2013). Improvements in glucose homeostasis following RYGB are associated with changes in FGF 19/15 (Pournaras *et al*. 2012, Sachdev *et al*. 2015), possibly via inhibitory effects on hepatic glucose production and lipogenesis through reductions in bile acid secretion (Gerhard *et al*. 2013). More recently, it has been shown that central FGF 19 improves glucose tolerance, suggesting a central role for the glucoregulatory action of FGF 19 (Morton *et al*. 2013, Ryan *et al*. 2013, Marcelin *et al*. 2014). These studies, therefore, suggest that synthetic FXR agonists could act as potential diabetic treatments. Indeed, obeticholic acid, a semisynthetic FXR agonist, improves insulin sensitivity in type 2 diabetic patients (Mudaliar *et al*. 2013), while GW4064 has been shown to prevent insulin resistance in rodents (Ma *et al*. 2013). Furthermore, treatment with a gut-specific FXR agonist, fexaramine, reduces diet-induced increases in hepatic glucose production in mice, likely due to a robust increase in FGF 15 (Fang *et al*. 2015). In contrast, some studies suggest that intestinal inhibition of FXR may in fact be beneficial via a reduction in intestinally derived ceramides (Li *et al*. 2013, Jiang *et al*. 2015), or via increased GLP-1 signalling (Trabelsi *et al*. 2015), warranting further research into FXR agonism/antagonism for the treatment of diabetes. Interestingly, it has also been proposed that FXR-mediated metabolic improvements are due to alterations of the gut microbiota (Ryan *et al*. 2014).

Gut microbiota

The gut microbiota, which contains an estimated 100 trillion cells consisting of over 1000 different species of known bacteria, has a major influence on host energy homeostasis, and diabetes is associated with changes in both the bacterial composition and genetic make-up (see for review on gut microbiota and diabetes (Duca & Lam 2014, Tilg & Moschen 2014)). Meanwhile bariatric surgery drastically alters the composition and diversity of the gut microbiota in humans, rats and mice (Zhang *et al*. 2009, Furet *et al*. 2010, Li *et al*. 2011*a*, Liou *et al*. 2013, Osto *et al*. 2013, Ryan *et al*. 2014, Tremaroli *et al*. 2015, Yang *et al*. 2015). Interestingly, germ-free (GF) mice colonized with the microbiota derived from humans, who had underwent RYGB or vertical banded gastroplasty exhibited reduced fat deposition when compared with GF mice colonized with the microbiota of obese controls (Tremaroli *et al*. 2015). This is in line with the fact that GF animals inoculated with the gut microbiota of RYGB-treated mice gained less weight and have a trend towards improved insulin sensitivity when compared with GF mice receiving sham microbiota (Liou *et al*. 2013).

Although the mechanisms for gut microbiota-mediated improvements in glucose homeostasis are still not completely understood (Duca & Lam 2014, Tilg & Moschen 2014), alterations in short-chain fatty acid (SCFA) production via fermentation of nondigestible polysaccharides has been hypothesized (Vrieze *et al*. 2012, Liou *et al*. 2013). For example, in the RYGB microbiota transplant study described above, levels of propionate were increased in both the RYGB-treated donor and the recipient mice (Liou *et al*. 2013). Indeed, supplementation with propionate or fermentable fibre is known to reduce appetite and improve glucose tolerance, possibly from inducing distal intestinal gut peptide secretion

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(Everard *et al*. 2011, Lin *et al*. 2012, Chambers *et al*. 2015, Psichas *et al*. 2015*b*). Ileal propionate activates mucosal FFAR2 to lower hepatic glucose production through a GLP-1-dependent neuronal pathway (Zadeh-Tahmasebi *et al*. 2016), while increased concentrations of SCFA in the large intestine have been shown to increase circulating levels of GLP-1 and PYY and reduce postprandial insulin and glucose levels (Tolhurst *et al*. 2012, Psichas *et al*. 2015*b*). As such, it is possible that improvements in glucose homeostasis following RYGB are due, at least in part, to changes in the production of SCFA in the ileum and large intestine. Although treatment with SCFAs is not feasible, as they are very unpalatable and do not reach the distal small and large intestine where they are endogenously produced, prebiotic treatment (nondigestible fibre) effectively increases distal intestinal SCFA production and improves glucose homeostasis in rodents (Cani *et al*. 2006*b*, Everard *et al*. 2011), which is thought to be mediated through an increase in gut peptide release (Cani *et al*. 2004, 2005, 2006*b*, Everard *et al*. 2011, Neyrinck *et al*. 2012). While some evidence exists for the beneficial effects of fermentable dietary fibre in humans (Archer *et al*. 2004, Cani *et al*. 2006*a*, 2009, Parnell & Reimer 2009), intake of dietary fibre is generally low (Howarth *et al*. 2003), and prebiotic treatment may not readily increase propionate production (Chambers *et al*. 2015). As such, a novel carrier molecule was developed to selectively increase colonic propionate levels. Treatment with this inulin-propionate ester for 24 weeks reduced weight gain and adipose distribution, and prevented the decrease in glucose tolerance and insulin sensitivity exhibited by the control group (Chambers *et al*. 2015). In addition, faecal microbiota transfer (FMT) represents another potential mechanism to increase SCFA levels and improve glucose homeostasis, as duodenal transfer of microbiota from lean humans into those with metabolic syndrome results in an increase in butyrate-producing bacteria and insulin sensitivity 6 weeks after the transfer (Vrieze *et al*. 2012). However, FMT is still experimental, and a more selective change in distal bacterial composition through pre- or probiotics may prove a safer and more efficacious option.

One of the more recently studied bacteria, *Akkermansia muciniphila*, might hold promise as a probiotic treatment for diabetes. *A. muciniphila* is a mucin-degrading, Gram-negative bacterium that resides in the mucus layer, and represents 3–5% of the microbial community (Derrien *et al*. 2004). Levels of *A. muciniphila* are inversely correlated with body weight, glucose tolerance and type 1 diabetes, while RYGB increases *A. muciniphila* abundance (Zhang *et al*. 2009, Hansen *et al*. 2012*a*, Everard *et al*. 2013, Liou *et al*. 2013, Shin *et al*. 2014, Schneeberger *et al*. 2015, Dao *et al*. 2016). Furthermore, reduced *A. muciniphila* levels in diet-induced obesity are normalized following prebiotic feeding, which is associated with improvements in metabolic dysregulation (Everard *et al*. 2013). In humans, *A. muciniphila* abundance is inversely related to fasting glucose and patients with increased *A. muciniphila* abundance and gene richness exhibited improved fasting plasma glucose levels and greater improvements in insulin sensitivity following caloric restriction (Dao *et al*. 2016). Direct chronic treatment in diet-induced obese mice with alive, but not heat-killed *A. muciniphila* reversed weight and fat mass gain, as well as insulin resistance (Everard *et al*. 2013). Further, chronic treatment with dietary phenols from grapes, or cranberry extract, improved glucose tolerance and insulin sensitivity which was hypothesized to be due to *A. muciniphila* abundance (Anhe *et al*. 2015, Roopchand *et al*. 2015). Although *A. muciniphila* remains to be tested in humans, this is one example in an ever-expanding list of potential probiotics that could help lower glucose levels in type 2 diabetes (Le Barz *et al*. 2015, Stenman *et al*. 2015*a*). It is interesting to note that metformin treatment has been shown to alter the gut microbiota, with chronic treatment resulting in *A. muciniphila* abundance, as well as changes in bile acid levels, suggesting a gut microbiota-mediated role for metformin treatment (Lien *et al*. 2014, Napolitano *et al*. 2014, Shin *et al*. 2014).

Metformin

As mentioned above, metformin is the first-line medication for the treatment of type 2 diabetes, as it potently reduces hyperglycaemia via a reduction in hepatic glucose production (Foretz *et al*. 2014). Although the main action of metformin was originally hypothesized to be due to activation of hepatic AMP-activated kinase (AMPK) (Shaw *et al*. 2005), an intracellular energy sensor, via increased AMP levels resultant from inhibition of the mitochondrial respiratory chain complex 1 (Owen *et al*. 2000), recent work has readily challenged that. Recent studies have demonstrated that metformin can lower HGP by: suppressing glycolytic enzymes in an AMPK-independent fashion (Foretz *et al*. 2010), antagonizing hepatic glucagon action (Miller *et al*. 2013), and via an alteration in mitochondrial and cytosolic redox states (Madiraju *et al*. 2014). Furthermore, the action of metformin in the gut has recently been identified to play a role in its glucose-lowering ability

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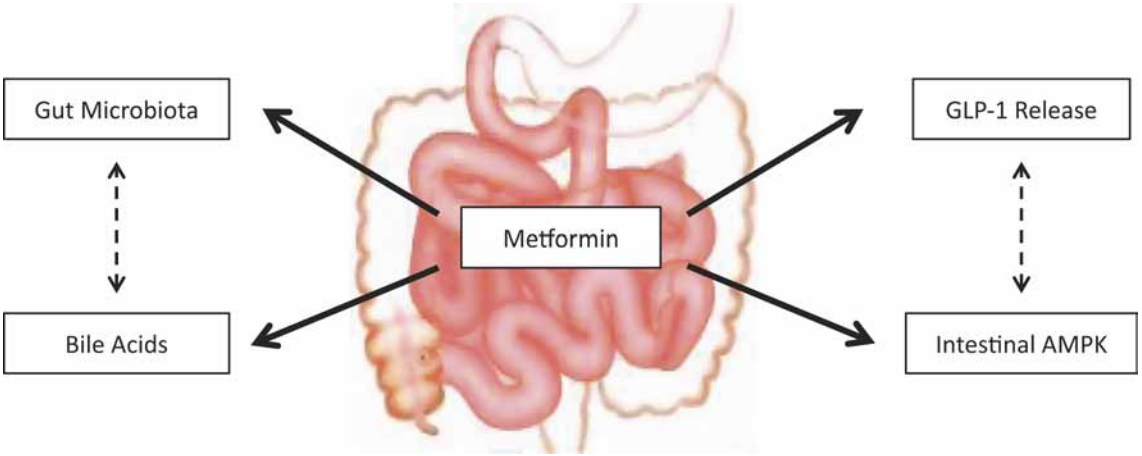

Figure 2
Intestinal actions of metformin potentially regulating glucose homeostasis. Metformin can act in the gut to alter gut microbiota and bile acids, which have been shown to contribute to glucose homeostasis. Furthermore, metformin increases GLP-1 release and can activate intestinal AMPK to lower glucose production possibly via increased GLP-1 signalling.

(Fig. 2). Indeed, oral/intestinal treatment of metformin results in a greater drop of blood glucose than IV or even portal treatment (Stepensky *et al.* 2002). Interestingly, delayed-release metformin, which is formulated to avoid absorption and target the lower bowel, was more effective at lowering fasting plasma glucose than currently available metformin (Buse *et al.* 2016). One possible mechanism may be in the ability of metformin to activate a gut–brain–liver axis to lower hepatic glucose production. Specifically, preabsorptive metformin activates small intestinal mucosal AMPK, triggering a GLP-1R-protein kinase A-dependent pathway to lower glucose production (Duca *et al.* 2015). This is in line with the fact that metformin can increase both acute and chronic levels of GLP-1 (Foretz *et al.* 2014). Interestingly, when small intestinal AMPK was virally knocked-down in diabetic rodents, the glucose-lowering ability of acute metformin treatment was diminished by about 50%, indicating a potent and sustained contribution of intestinal AMPK activation to metformin's effect (Duca *et al.* 2015). Additionally, this study highlights the potential for more direct targeting of intestinal energy sensors to treat diabetes. For example, in addition to AMPK, the NAD+-dependent deacetylase sirtuin 1 (SIRT1) is expressed in the small intestinal mucosa. Activation of small intestinal SIRT1, via intraintestinal resveratrol infusion, triggers a vagal gut–brain neuronal axis to improve hypothalamic insulin sensitivity to lower hepatic glucose production in high-fat-fed and diabetic rodents (Cote *et al.* 2015). Interestingly, this effect was also dependent on AMPK (Cote *et al.* 2015), indicating a possible interactive dependency between these two molecules, although it remains to be tested whether SIRT1 is required for intraintestinal metformin in the gut. Nonetheless, it may be efficacious to develop a 'gut-targeted' metformin-like molecule that could activate intestinal mucosal AMPK and/or other energy sensors to potently lower glucose levels in diabetic individuals, given that intestinal AMPK is reduced in diabetes (Harmel *et al.* 2014).

Conclusion

The metabolic potential of the GI tract is becoming increasingly recognized. Drugs aimed at mimicking gut-derived molecules, like GLP-1 receptor agonists, are readily being tested and used for diabetic treatment. As of now, most GLP-1R agonists are administered as a complimentary therapeutic option to metformin, but perhaps in the future, more specialized 'cocktail' treatments will be developed to provide a more complete action on complex signalling pathways that often compensate and limit long-term drug potential. Perhaps an even better approach will be to alter endogenous levels of gut-derived hormones, as is done with manipulation of bile acids and gut microbiota following bariatric surgery. Instead of surgery, drugs are also being developed to directly influence the gut milieu, like bile acid sequestrants and pre/probiotics. Although manipulation of a stable gut microbiota has proven difficult, with more research into how to effectively and favourably alter the microbiota in the long-term, pre/probiotics could be a valuable tool in

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treating diabetes, possibly as a combination with frontline treatments (Stenman *et al.* 2015*b*). Even more intriguing is the possibility that future treatments may involve genetically modified bacteria that contain therapeutic factors to help treat metabolic disease (Chen *et al.* 2014). Overall, the GI tract represents a promising avenue for the development of successful targeted therapeutic options for the treatment of diabetes.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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