Gut: a key player in the pathogenesis of type 2 diabetes?

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Abstract

The gut regulates glucose and energy homeostasis; thus, the presence of ingested nutrients into the gut activates sensing mechanisms that affect both glucose homeostasis and regulate food

intake. Increasing evidence suggest that gut may also play a key role in the pathogenesis of type 2 diabetes which may be related to both the intestinal microbiological profile and patterns of gut hormones secretion. Intestinal microbiota includes trillions of microorganisms but its composition and function may be adversely affected in type 2 diabetes. The intestinal microbiota may be responsible of the secretion of molecules that may impair insulin secretion/action. At the same time intestinal milieu regulates the secretion of hormones such as GLP-1, GIP, ghrelin, gastrin, somatostatin, CCK, serotonin, peptide YY, GLP-2, all of which importantly influence metabolism in general and in particular glucose metabolism. Thus, the aim of this manuscript is to review the current evidence on the role of the gut in the pathogenesis of type 2 diabetes, taking into account both hormonal and microbiological aspects.

Keywords

gut, microbiota, type 2 diabetes, obesity, environment, lifestyle, GLP-1, serotonin, Roux-y-gastric-by-pass, GIP

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Introduction

The gut is traditionally seen as an organ that mediates nutrients digestion and absorption through the release of hormonal and neural regulatory signals in response to nutrient intake (Breen at al.,2013). Recent results indicate that gut can sense nutrient influx and, in turn, adjust endogenous glucose production and food intake, thus maintaining metabolic homeostasis in the face of nutritional challenge (Breen at al., 2013). A number of modifications in gastrointestinal function, reported in obese subjects, may potentially be dependent of the gastrointestinal adaptation to high nutrient exposure (Little et al., 2007). Surgical manipulation of the intestine (as after gastric bypass operations) has been demonstrated to have dramatic effect on glucose metabolism, independent of weight loss, leading to the hypothesis that gut produces and releases key factors for the regulation of glucose metabolism (Rubino et al.,2012). In addition recent evidence highlights the role of gut microbiota as an important environmental factor in the pathogenesis of type 2 diabetes (T2D) (Burcelin et al., 2011; Nicholson et al., 2012). The human microbiota is composed of trillions of microorganisms, including more than 2000 species of commensal bacterial organisms which are thought to contribute importantly to metabolic homeostasis (Neish 2009). Both the composition and function of the gut microbiota have been reported to be affected in subjects with diabetes. Moreover, the endocrine functions of the gut also seem to be affected in T2D. In type 2 diabetic individuals, including those with prediabetes, meal-stimulated GLP-1 secretion is generally impaired (Faerch et al., 2015). In rats, hyperglycaemia downregulates GLP-1 receptor expression on beta cells resulting in ‘GLP-1 resistance’. Thus, the diabetic beta cells display a resistance to physiological levels of endogenous GLP-1 (Hojberg et al., 2009). Moreover, a relevant number of type 2 diabetic

subjects exhibit a normal GLP-1 secretion, particularly after an oral glucose tolerance test, despite an impaired insulin secretion, suggesting resistance to GLP-1 in human (Bagger et al.,2011; Knop et al.,2007). Additional studies in type 2 diabetic subjects have revealed an impairment of both GIP secretion and function, as well (Crockett et al.,1976; Meier et al.,2004).

Thus, the aim of this review is to focus on the gut, evaluating both microbiological and hormonal changes that may take part in the complex interplay that leads to the onset of T2D.

Type 2 diabetes and gut microbiota

T2D is an increasingly prevalent chronic metabolic disorder characterized by hyperglycemia; The WHO's first global report on diabetes shows that 422 million adults were living with diabetes in 2014 (Global report on diabetes). World Health Organization, Geneva, 2016. This condition is known to result in gastrointestinal dysbiosis involving both compositional and functional changes in the gut microbiota (He et al.,2015). In fact, the gut microbiota represents a key factor in the regulation of different metabolic pathways (Cani et al., 2014) playing an important role in glucose hemostasis and T2D pathogenesis (Egshatyan et al., 2016; Sekhar et al.,2015).

Type 2 diabetes and gut microbiota: Evidence from experimental animal studies

Experimental animal studies suggest that metabolic disorders, including diabetes, are associated with changes in the composition and metabolic function of gut microbiota. Bäckhed et al. hypothesized that gut microbiota might contribute to alterations in glucose metabolism performing experiments in germ-free mice (Backhed et al., 2004). Next, several studies reported

significant differences between gut microbiota between diabetic and non diabetic animals. In particular, diabetic obese leptin-resistant mice (db/db) showed a significantly higher abundance of Firmicutes, Proteobacteria, and Fibrobacteres phyla compared to lean mice (Geurts et al.,2011). Other studies in mice have corroborated these results (Turnbaugh et al.,2008; Turnbaugh et al., 2009; Fleissner et al.,2010; Hildebrandt et al., 2009). Interestingly, some probiotic strains are able to modulate the glucose homeostasis, and hence to improve T2D management (Panwar et al., 2013). Several mechanisms have been proposed to explain the possible relationships between probiotics, glycemic control and other diabetes-related outcomes. Recently, it has been hypothesized that the positive effects of probiotics on glucose metabolism could be mediated by the increased expression of insulin signaling proteins, the improvement in adipokine profile, and the prevention of weight gain and glucose intolerance (Mazidi et al., 2016) (Figure 1). More specifically, Yakovlieva et al. studied rats assigned to receive a standard diet (Con, control group), fructose-enriched diet (Fr group), standard diet with probiotics given twice a week (Pro group), and fructose-enriched diet with probiotics given twice a week (Pro+Fr group). Probiotics were Bulgarian Lactobacillus strains, Lactobacillus brevis 15 and Lactobacillusplantarum 13. They found that the highest elevation of blood glucose levels was observed in the Fr group, followed by the Pro+Fr group, whereas the Pro group showed the lowest levels (0.60 mmol/l) (Yakovlieva et al., 2015). In addition, Bifidobacterium animalis ssp. lactis 420 has been shown to reduce fat mass and glucose intolerance in both obese and diabetic mice (Stenman et al., 2014). Similarly, Le et al. found that in C57BL/6J mice with streptozotocin-induced diabetes oral administration of Bifidobacterium spp. reduced blood glucose levels and increased the protein expressions of insulin receptor beta, insulin receptor

substrate 1, protein kinase B (Akt/PKB), IKKα, and IκBα. Also, Bifidobacterium spp. induced the adiponectin expression and decreased both macrophage chemoattractant protein-1 and interleukin-6 expression (Le et al., 2015).

Type 2 diabetes and gut microbiota: Evidence from experimental humans studies

Several studies have shown that the composition of the gut microbiota differs between T2D patients and non-diabetic individuals (Karlsson et al., 2016). In particular, T2D in humans is associated with modifications of the normal local distribution of microbial communities characterized by the presence of a low percentage of bacterial Firmicutes and Clostridia species (Larsen et al., 2010). In addition, it has been suggested that butyrate produced by certain bacteria prevents translocation of endotoxic compounds derived from the gut microbiota, which have been shown to drive insulin resistance (Utzschneider et al., 2016). In 2016, Pedersen et al. found that in 277 non-diabetic Danish individuals levels of branched-chain amino acids (BCAAs), which are increased in the serum metabolome of insulin-resistant individuals, correlate with a gut microbiome that has an enriched biosynthetic potential for BCAAs and is deprived of genes encoding bacterial inward transporters for these aminoacids. Prevotella copri and Bacteroides vulgatus are identified as the main species driving the association between biosynthesis of BCAAs and insulin resistance (Pedersen et al., 2016). A direct link between an altered gut microbiota and T2D was recently provided also by experiments of transplantation with intestinal microbiota from lean healthy donors. In particular, Vrieze et al. reported the increase in insulin sensitivity and levels of butyrate-producing bacteria increased in patients with the metabolic syndrome after infusion of microbiota from lean healthy donors (Vrieze et al., 2012). The infusion of microbiota from lean healthy to diabetic subjects, was associated to the improvement

of metabolic control in T2D (Kootte et al., 2012). A recent meta-analysis, which assessed the effect of probiotic supplementation on metabolic profiles in T2D by considering 12 randomized controlled trials, showed that probiotics could alleviate fasting blood glucose and increase high-density lipoprotein-cholesterol, whereas no significant differences in low-density lipoprotein-cholesterol, total cholesterol, triglyceride, HbA1c and HOMA index between the treatment group and the control group was found (Li et al., 2016).

Recent metagenomics approaches have investigated whether the gut microbiota is altered in patients with T2D. Shotgun sequencing of the gut metagenome revealed that butyrate-producing bacteria, known to be anti-inflammatory, as well as clostridial cluster XIVa including Roseburia spp. and Faecalibacterium spp., are less abundant in T2D patients than in healthy control subjects (Li et al., 2016; Karlsson et al.,2013) (Figure 1).

Endocrine regulation

The intestinal endocrine cells produce hormones involved in regulation of digestion, metabolism and appetite. The incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) stimulate insulin secretion and regulate postprandial glucose excursions, while GLP-1, cholecystokinin (CCK), and peptide YY (PYY) inhibit appetite and food intake. In contrast, ghrelin, secreted from the stomach acts as a nutrient sensor signaling to the brain, increasing the motivation to eat (Muller et al., 2016). The incretin hormones are required to maintain an adequate islet number in adulthood and to maintain normal beta cell responses to glucose both in vitro and in vivo; in fact, it is estimated that up to 70% of the insulin secretion in response to an oral glucose load is mediated by the actions of the incretin hormones,

an observation referred to as the “incretin effect”; moreover, it is well known that in patients with T2D, the incretin effect is clearly reduced (Nauck et al., 1986). An intestinal epithelial-specific ablation of Isl1, a transcription factor expressed specifically in a number of intestinal endocrine cells, including incretin-expressing cells, results in loss of GLP-1, GIP, CCK, and somatostatin-expressing cells and an increase in 5-HT (serotonin)-producing cells. This dramatic change in hormonal milieu results in impaired glucose tolerance when the animals are challenged only with oral andnot with intraperitoneal glucose,, indicating loss of the incretin effect (Terry et al., 2014). Thus, any derangement of the enteroendocrine system might lead to or accelerate the development of T2D (Table 1).

CCK

CCK is a peptide hormone produced in the gut and brain with important effects on digestion and appetide regulation. Selective agonists of CCK receptor have been shown to significantly reduce glycated haemoglobin and food intake in a high fat fed mouse model (Irwin et al., 2013) especially when co-administered with exendin-4 (Irwin et al., 2013) or GIP (Irwin et al., 2013). CCK-1 receptor deficient Otsuka Long Evans Tokushima Fatty (OLETF) rats represent an animal model of hyperphagia, which leads to obesity and diabetes. In previous studies, these animals exhibited increased oil and sucrose intake presumable driven by both deficits in both peripheral satiation mechanisms and altered oro-sensory sensitivity (De Jonghe et al., 2005). Noteworthy, CCK has been shown to be expressed also in pancreatic β-cells, but only in models of obesity and insulin resistance (Lavine et al.,2015); moreover, CCK appeared the most up-regulated gene in obese pancreatic islets (Lavine et al., 2010). Interestingly, beta-cell

proliferation, up-regulation of distinct set of cell cycle regulators in islets, and signals induced by CCK may partially be independent by its own receptors (Lavine et al., 2008). Together this could suggest that CCK signaling impairment should be analyzed in order to highlight possible mechanistic association with development of T2D. It has been demonstrated that in humans CCK delays gastric emptying and slows the delivery of glucose to the duodenum, thus reducing postprandial hyperglycemia (Liddle et al., 1988). In addition, CCK seems to reduce meal duration and the quantity of the ingested food, consistently with the hypothesis that CCK is an endogenous signal for postprandial satiety (Kissileff et al., 1981). This is also in accordance with the relationship found in dialysis patients of fasting CCK with variability of the hunger and fullness scores (Wright et al., 2004). In addition, in healthy subjects, it has been shown that CCK infusion augmented arginine-stimulated insulin levels, thus demonstrating that physiological concentrations of CCK potentiate amino acid-induced insulin secretion in man (Rushakoff et al., 1987) although a role for CCK in regulation of insulin secretion is not supported by all studies. Also in T2D, effects of the hormone on the regulation of postprandial hyperglycemia and on the secretion of insulin have been reported (Rushakoff et al., 1993; Ahrén et al., 2000). Dysregulation of the CCK response to test meal has been described in patients with T2D, even if contradictory results have also been reported. In fact, some authors showed that the ingestion of a test meal in diabetic subjects caused a significantly greater increase of plasma CCK than in healthy ones (Nakano et al., 1986). Conversely, other authors found that the plasma CCK response to feeding was blunted in the patients compared to the one of controls (Rushakoff et al., 1993). In addition, a possible involvement of this hormone in the metabolic disorders leading to

T2D was also supported by the correlation of CCK with leptin and insulin in type 2 diabetic patients (Milewicz et al., 2000).

Gastrin

The gastrointestinal peptide gastrin is an important regulator of the release of gastric acid from the gastric parietal cells and has been reported to play an important role in β-cell regeneration. In fact, in rat and mouse models, gastrin treatment significantly increased β-cell mass, increased β-cell neogenesis and resulted in β-cell mass expansion, dedifferentiation and reprogramming of regenerative ductal cells, improving glucose tolerance (Sasaki et al.,2015; Suarez-Pinzon et al., 2008; Tellez et al. 2011; Tellez et al., 2014). The effects of treatment with gastrin on β-cell appear even more pronounced when combined with either GLP-1R agonists (Fosgerau et al., 2013; Suarez-Pinzon et al., 2008) or epidermal growth factor (Rooman et al., 2004; Song et al., 2015). Interestingly, overexpression of GLP-1R, together with gastrin and exendin-4, synergistically promoted beta cell neogenesis accompanied by the formation of islet-like clusters (Sasaki et al., 2015). In humans, gastrin-releasing peptide seems to produce a significant reduction in calorie intake together with less hunger and early fullness in the premeal period (Gutzwiller et al., 1994). In addition, in healthy subjects, gastrin administration results in the increase of insulin concentration (Rehfeld et al., 1971; Rehfeld et al., 1973; Dupre et al., 1969). This favorable effect has been also indirectly evaluated in some studies by testing the possible anti-diabetic effect of proton-pump inhibitors, which increase gastrin levels. In particular, a 12-wk, randomized, double-blind, placebo-controlled administration of pantoprazole in patients with T2D, showed significantly increased plasma gastrin and insulin levels and improved β-cell function, along with a significant decrease in HbA1c. Of note, the decrease in HbA1c correlated

with the increase of gastrin and insulin (Singh et al., 2012). Similarly, another clinical trial, which assessed drug-naïve adults (30- to 60-years of age) with T2D, found significant increases in late and total insulin secretion after pantoprazole administration together with a significant decrease in HbA1c (Gonzalez-Ortiz et al., 2015). A beneficial effect of proton-pump inhibitors is also supported by other clinical studies (Inci et al., 2014; Mefford et al., 2012). A study evaluating patients with type II diabetes and autonomic neuropathy, diabetic patients without autonomic neuropathy, and healthy subjects found that gastrin plasma concentrations were basally higher in patients with diabetes with autonomic neuropathy. After food intake, gastrin plasma concentrations increased within 30 minutes in all groups but to a greater extent in patients with diabetes with autonomic neuropathy, thus suggesting that in patients with type II diabetes with autonomic neuropathy, food is emptying more slowly from the stomac resulting in increased plasma gastrin level responses (Migdalis et al., 2001). It is likely that there are differences in the responses to food ingestion between these groups because of vagal damage associated with autonomic neuropathy (Migdalis et al., 2001). In addition, in patients with T2D, during food intake the levels of gastrin rise, whereas they do not change during glucose tolerance test. A rise of the level of gastrin in diabetic subjects during a test breakfast was accompanied by changes in the level of insulin, but peak values were lower than during oral glucose tolerance test (OGTT) (Starosel'tseva et al., 1988).

Ghrelin

Circulating ghrelin is produced predominantly in the stomach and to a lesser extent in the intestine, pancreas and brain. Ghrelin, initially identified as a potent stimulator of growth hormone release and food intake, has been shown to suppress glucose-induced insulin release

(Tong et al., 2010). Ghrelin is O-octanoylated at Ser3 (acylated ghrelin) by the enzyme ghrelin O-acyltransferase (GOAT), a posttranslational modification required for its actions through growth hormone secretagogue receptor 1a (GHS-R1a). However, as only 5--20% of circulating ghrelin is acylated, unacylated ghrelin (UnAG, also called desacyl-ghrelin) remains the major circulating form (Kojima et al., 2005). Ghrelin is a peptide hormone that has unique orexigenic properties. By acting on the GHS-R1a, ghrelin induces a short-term increase in food consumption, which ultimately induces a positive energy balance and increases fat deposition (Camilleri et al., 2009). Ghrelin also seems to promote the survival of pancreatic β-cells by mechanisms other than ghrelin-receptor activation; administration of ghrelin, in fact, reduced apoptosis in a pancreatic β-cell line via MAPK--PI3K pathways (Zhang et al., 2007). Ghrelin and unacylated ghrelin also promoted proliferation and inhibited β-cell apoptosis in a β-cell line and in human islets of Langerhans via cAMP--PKA, ERK1--ERK2, and PI3K--Akt signaling pathways (Granata et al., 2007). However, ablation of ghrelin signaling has been associated to an improvement of glucose tolerance and enhances insulin secretion in leptin-deficient ob/ob mice (Sun et al., 2006). Several lines of evidence indicate that unacylated-ghrelin counteracts the effects of ghrelin on insulin secretion. Negative findings from studies of isolated mouse and rat pancreatic islet cells suggest that unacylated ghrelin regulates glucose metabolism without affecting hormone secretion by the pancreas. From studies of a combination of acylated and unacylated ghrelin in 10-fold higher conentrations given to isolated islet cells of rodents suggested that the un-acylated form inhibits the ability of ghrelin to reduce insulin secretion (Vamvini et al., 2016). Finally, unacylated-ghrelin has been reported to inhibit glucose output

from isolated pig hepatocytes and to counteract the stimulatory effect of ghrelin on hepatocyte glucose output (Gauna et al., 2005).

In a randomized double-blind cross-over study in nine healthy volunteers, intravenous ghrelin infusions were demonstrated to increase food intake from a free-choice buffet compared with saline infusion. Similarly, visual analogue scores for appetite were greater during ghrelin compared to saline infusion (Wren et al., 2001). In addition, in ten healthy subjects, plasma ghrelin levels increased nearly twofold immediately before each meal and fell to trough levels within 1 hour after eating, thus suggesting that ghrelin plays a physiological role in meal initiation (Cummings et al., 2007). Also, in healthy subjects the consumption of food for pleasure was characterized by preceeding increases in peripheral ghrelin levels (Monteleone et al., 2012) and the increase in evening ghrelin during sleep restriction was correlated with higher consumption of calories from sweets (Broussard et al., 2016). As far as glucose homeostasis is concerned, in healthy humans, ghrelin seems to have hyperglycemic effect and to lower insulin secretion. In fact, ghrelin administration to healthy young volunteers induced a prompt increase in glucose levels and a decrease in serum insulin levels (Broglio et al., 2001). Also, in young volunteers 16 hour-acylated ghrelin infusion (from 21:00 to 13:00) increased the glucose responses to both dinner and breakfast and blunted the early insulin response to dinner (Broglio et al. 2008). Similar findings were made in a large population-based study comprising 2082 subjects with no serious metabolic, cardiovascular, or endocrine diseases in which correlation analyses showed a significant negative relationship between circulating ghrelin and insulin levels (Amini et al., 2012). On the other hand, in type 2 diabetic subjects, ghrelin concentrations were found to be significantly lower compared with those of nondiabetic subjects (Erdmann et al.,

2005) and were negatively associated with fasting insulin as well as prevalence of T2D and insulin resistance (Poykko et al., 2003). Also, in T2D, negative correlations of plasma ghrelin with BMI, visceral, subcutaneous and total fat area (Katsuki et al., 2004) and glycated hemoglobin (Ueno et al., 2007) were demonstrated, suggesting a suppressing effect of these factors on ghrelin levels. In addition, insulin reduces plasma ghrelin to a lesser extent in type 2 diabetic patients before insulin therapy compared to nondiabetic patients (Anderwald et al., 2003).

GIP

Enteroendocrine K cells secrete the incretin hormone glucose-dependent insulinotropic peptide (GIP), and are predominately located in the duodenum and the proximal smal intestine. GIP is a peptide hormone which potentiates glucose-stimulated insulin secretion during a meal. While GLP-1 decreases glucagon levels, GIP enhances glucagon secretion at least at lower plasma glucose levels (Christensen et al., 2015). GIP exert its effects by binding to their specific receptors, the GIP receptor, which belong to the G-protein coupled receptor family. Receptor binding activates and increases the level of intracellular cAMP in pancreatic β cells, thereby stimulating insulin secretion glucose-dependently (Yabe et al., 2011). GIP has the potential to ameliorate glucose intolerance even after STZ-induced beta cell damage by increasing insulin secretion rather than by promoting beta cell survival (Iida et al., 2016). Moreover, GIP, given to achieve supraphysiological plasma levels, has been shown to have an early, short-lived insulinotropic effect in T2D. However, because glucagon secretion may also be enhanced (in spite of diabetic hyperglycaemia), the glucose-lowering effect of GIP is abolished. In this way, GIP may actually worsen hyperglycemia post-prandially (Chia et al., 2009). These findings make

it unlikely that GIP or GIP receptor agonists would be suitable in treating the hyperglycemia of patients with T2D (Chia et al., 2009). However, several studies regarding GIP have focused on its insulinotropic actions and other β-cell functions, and long-term administration of DPP-IV resistant GIP analogues showed marked improvements in glucose tolerance in normal and diabetic rats, as well as in high fat (HF) fed mice (Gault et al., 2011; Hinke et al. 2002; Kim et al., 2012). Additionally, subcutaneous administration of D-Ala2-GIP1--30 to Zucker diabetic fatty rats had potent anti-diabetic effects that included reduced β-cell apoptosis and improved β-cell function and glycemic control (Widenmaier et al., 2010). In diabetic mice, a novel N- and C-terminally modified GIP analogue (AC163794) improved HbA1c through enhanced insulinotropic action, partial restoration of pancreatic insulin content and improved insulin sensitivity with no adverse effects on fat storage and metabolism. These studies support the potential use of the GIP analogue for the treatment of T2D (Tatarkiewicz et al., 2014). The role of GIP in regulating glucose homeostasis has been also assessed in diphtheria toxin-expressing (DT) mice that specifically lack GIP-producing cells (Pedersen et al., 2013; Zhang et al., 2013; Zhang et al., 2015). In these studies, even though Pedersen et al. suggested that K cells are less involved in acute regulation of mouse glucose metabolism than L cells and α-cells, Zhang et al demonstrated a lack of incretin response, even with a preserved GLP-1 release. Moreover, with high-fat feeding, DT mice remained lean but developed T2DM, whereas wild-type mice developed obesity but not diabetes. Metabolomics evaluation identified increased β-hydroxypyruvate as a possible mediator of T2D development. In fact, in vitro, β-hydroxypyruvate altered excitatory properties of myenteric neurons and reduced islet insulin content but not glucose-stimulated insulin secretion. Thus, K cells may maintain long-term

function of neurons and β-cells by regulating β-hydroxypyruvate levels (Zhang et al., 2013; Zhang et al., 2015). Studies showing that homozygous GIP receptor knockout (KO) mice (GIPRKO) were resistant to obesity when fed a HF diet (Miyawaki et al., 2002) and the presence of K-cell hyperplasia and elevated GIP and insulin levels in HF fed rodents, led to the suggestion that GIP may contribute to the development of obesity, with associated insulin resistance and glucose intolerance (Gniuli et al., 2010; Irwin et al., 2009). Consequently, it has been proposed that GIP antagonist treatment, reducing circulating GIP levels with K-cell ablation (Althage et al., 2008) or vaccination against GIP (Fulurija et al., 2008) may be beneficial treatments for obesity. However, the question as to whether long-term elevation of GIP production causes detrimental pro-obesity effects has not been directly addressed and we have therefore examined responses of transgenic overexpression of GIP mice to HF diet feeding. The results demonstrate that, in contrast to expectations, transgenic overexpression of GIP had major beneficial effects on both glucose and fat metabolism (Kim et al., 2012).

In healthy subjects, GIP has been shown to minimally affect gastric half-emptying time, hunger, desire to eat or satiety (Edholm et al., 2010). The peptide seems to jor contribute importantly to the incretin effects in concert with the several-fold increase of its plasma levels after the administration of oral glucose in healthy volunteers (Nauck et al., 1993). In healthy subjects, robust evidence supports that GIP infusion induces insulin increase (Asmar et al., 2010; Sarson et al., 1984; Meier et al.,2004). In contrast, in T2D, a loss of incretin activity of GIP occurs. In fact, in subjects with T2D, following GIP infusion, insulin and c-peptide increased far less than in normal subjects (Jones et al., 1987; Nauck et al., 1993). Also, diminished GIP-effects were found in first-degree relatives of patients with T2D compared with controls (Meier et al., 2001).

These findings have suggested the hypothesis that a specific defect in GIP action, possibly at the level of the GIP receptor, might precede the development of T2D (Meier et al., 2004). However, the preservation of a relative sensitivity of insulin secretion to GIP bolus in patients with T2D, even though at a lower level of β-cell function, renders this hypothesis unlikely (Vilsboll et al., 2002). In addition, GIP has been shown to have glucagonotropic activities, both in healthy subjects and in type 2 diabetic subjects (Gault et al., 2011; Meier et al., 2003). In T2D, basal GIP levels have been reported to be higher (Crockett et al.,1976) or equal (Skrha et al., 2010) compared to those of control subjects. In addition, the area under curve of GIP during meal stimulation has in some studies been found to be significantly lower in subjects with T2D than in non-diabetic subjects, thus indicating an impaired GIP secretion and effect in T2D (Skrha et al., 2010; Groop et al., 1985).

GLP-1

In healthy humans, the incretin glucagon-like peptide 1 (GLP-1) is secreted after eating and lowers glucose concentrations by augmenting insulin secretion and suppressing glucagon release. Additional effects of GLP-1 include retardation of gastric emptying, suppression of appetite and possibly preservation of β-cell survival e.g. by inhibiting apoptosis. L-cell density and turnover do not seem to differ between patients with and without diabetes. Thus, alterations in the number of GLP-1 producing cells do not seem to explain the reduced incretin effect in patients with T2D (Kampmann et al., 2016). Chronic consumption of a high-fat diet did not change the pharmacokinetics of Ex4 but increased intestinal GLP-1R expression and decreased hindbrain GLP-1R expression (Mul et al., 2013). To determine whether the ability of endogenous GLP-1 to promote satiation is impaired by HF maintenance, we examined the response to exendin 3

(Bagger et al.,2011; Lavine et al., 2010) (Ex9), a GLP-1 receptor antagonist. In rats maintained on a low fat diet (LF-rats), Ex9 increased intake significantly, but HF-maintained rats had reduced food intake in response to Ex9. These data support the suggestion that maintenance on HF diet reduces the anorexic effects of GLP-1 receptor activation, and this phenomenon may contribute to overconsumption of high-fat foods (Williams et al., 2011). GLP-1 and its analogs may preserve pancreatic beta-cell mass by promoting resistance to cytokine-mediated apoptosis (Natalicchio et al., 2010; Natalicchio et al., 2013). We provided evidence that the GLP-1 receptor agonist, exendin-4, protects insulin-secreting cells from TNFα-induced apoptosis by inhibiting JNK signaling and the consequent proapoptotic response. Additionally, exendin-4 increased expression of IRS-2 and the activity of the IRS/Akt survival pathway in insulinoma cell lines, confirming the existence of a cross talk between G protein-coupled receptors and tyrosine kinase receptors (Natalicchio et al., 2010). Administration of GLP-1 was associated with proliferative and antiapoptotic effects in both endocrine and exocrine compartments of the pancreas (Bulotta et al., 2004; Farilla et al., 2002), and significantly reduced apoptotic beta cells in experimental diabetes models (Li et al., 2003). In an earlier study, Ling et al. showed that GLP-1 receptor (GLP-1R) knockout mice display normal β-cell mass (Ling et al., 2001). However, β-cell recovery after partial pancreatectomy appear reduced in GLP-1R knockout mice (De Leon et al., 2003), possible due to a diminished GLP-1 effect on β-cell mitogenesis; moreover, a loss of the action of both GLP-1 and GIP receptors (double incretin receptor knock-out mice) resulted in impairment of beta cell function both in vivo and in vitro in a process that appears to be independent of the intestinally secreted incretin hormones (Omar et al., 2016). It has been demonstrated that β-cell mass in leptin-receptor deficient ob/ob mice that also are GLP-

1R-deficient was comparable to that of ob/ob controls (Scrocchi et al., 2000), suggesting that although leptin and GLP-1 actions overlap in the brain and endocrine pancreas, disruption of GLP-1 signaling does not modify the response to leptin or the phenotype of leptin deficiency in the ob/ob mouse. This may occur because leptin-resistant and leptin-deficient animals have reduced intestinal GLP-1 secretion and plasma GLP-1 concentrations (Anini et al., 2003). Because obesity is linked to abnormal leptin signaling, it could be argued that leptin may modulate GLP-1 secretion. Therefore, obesity emerges as leptin resistance state and a relatively GLP-1-deficient state, where there is insufficient endogenous GLP-1 to expand β-cell mass. In T2DM, GLP-1 secretion is generally impaired, and this defect appears to be a consequence rather than a cause of impaired glucose homeostasis. Glucotoxicity diminishes the secretory responsiveness of GLP-1-secreting cells to acute glucose stimulation. We conclude that the loss of the incretin effect, as observed in T2DM patients, could at least partially depend on impaired glucose regulation, which is typical in diabetes patients (Urbano et al., 2016). Changes in the pattern of gut hormone secretion after bariatric surgery are thought to play a major role for the beneficial effect of this operation on glucose homeostasis, but the mechanisms leading to both changed hormone secretion and beneficial effects remain unclear. High concentrations of GLP-1 are encountered in the immediate postprandial period in patients with upper gastrointestinal surgery including gastric bypass surgery (De Luis et al., 2003; Vella et al., 2013). Noteworthy, in non-obese diabetic rodents, a stomach-sparing bypass of the duodenum and 20% of the jejunum did not cause weight loss, but improved fasting glucose, insulin action, and oral glucose tolerance (Rubino et al., 2005). When foregut exposure to nutrients was reversed after RYGB, the improvement in glucose metabolism was abrogated (Shimizu et al., 2014). This has been

interpreted to support that exposure of the foregut to intraluminal calories leads to elaboration of a diabetogenic mediator, unidentified so far. According to an alternative hypothesis the increased and earlier delivery of calories to the jejunum/ileum increases entero-endocrine secretion, most notably that of GLP-1, which consequently leads to improved insulin secretion and several other beneficial effects on glucose metabolism (Cummings et al., 2007). Numbers of incretin-immunoreactive cells appear significantly increased in the Roux and common limbs, but not the biliopancreatic limb in RYGB rats compared with sham-operated, obese rats fed high-fat diet, and chow-fed controls. This increase was mostly accounted for by general hyperplasia of all intestinal wall layers and less to increased density of expression (Mumphrey et al., 2013). However, whether changes in the number of hormone-secreting enteroendocrine cells, or changes in the releasing stimuli, or both, are important, needs to be elucidated. In a patient with diabetes operated with gastric bypass feeding of the same meal on two consectuive days, one day via the oral route (i.e. following the bypass) and on the second day via a gastrostomy catheter, and exaggerated hormone secretion and diabetes resolution was observed only on the first day, supporting that it is the surgical rerouting rather than adaptive increases that are responsible (Dirksen et al., 2010). Both in healthy subjects and people with T2D, GLP-1 decelerate gastric emptying, thus contributing to slow down the absorbed amount of glucose after meal ingestion (Wettergren et al., 2010; Nauck et al., 1997; Willms et al., 1996). GLP-1 inhibits antro-duodenal contractility and stimulated the tonic and phasic motility of the pylorus (Schirra et al., 2000). Moreover, GLP-1 has been demonstrated to enhance insulin release and significantly reduce peak plasma glucose concentrations during an intravenous glucose load in normal volunteers (Kreymann et al., 1987). In addition, this hormone lowers plasma glucagon concentrations

(Kreymann et al., 1987). Indeed, a normalization of glucose concentration by GLP-1 may be observed in T2D subjects; in addition, in these patients, a significant improvement in the insulin secretory response to glucose has been described (Rachman et al., 1996; Rachman et al., 1997). A reduction of plasma glucagon concentration has also been shown in T2D subjects (Nauck et al., 1993). In addition, GLP-1 reduces food intake, and elicits satiety and fullness in healthy subjects and patients with T2D (Flint et al., 1998; Gutzwiller et al., 1999; Meier et al., 2002). In patients with T2D, fasting intact GLP-1 levels have been found to be lower (Lastya et al., 2014; Legakis et al., 2003) or equal (Lee et al., 2010) than those of healthy subjects. However, the meal-related glucagon-likep peptide-1 response in T2D is decreased compared to control subjects (Toft-Nielsen et al., 2001; Visboll et al., 2001). Reduction of GLP-1 response in T2D compared to individuals with normal glucose tolerance is also evident after oral glucose tolerance test (Faerch et al., 2015; Bagger et al.,2011).

GLP-2

GLP-2 is formed from proglucagon in the intestinal L-cells and is secreted postprandially in parallel with the insulinotropic hormone GLP-1, which in addition acts to inhibit gastrointestinal motility by inhibiting central parasympathetic outflow. However, even though it may play a role the regulation of glucose homeostasis (Bahrami et al., 2010; Shi et al., 2013), GLP-2 does not seem to modulate insulin secretion (Orskov et al.,1988; Schmidt et al., 1985). Moreover, recent studies have shown that perfusion of isolated rat pancreas with GLP-2 resulted in increased glucagon secretion with no effect on insulin or somatostatin secretion (Sorensen et al., 2003). The actions of GLP-2 are transduced by the GLP-2 receptor (GLP-2R), which is localized mainly in the neurons of the enteric nervous system, indicating an indirect mechanism of action

and in subepithelial myofibroblasts (Baldassano et al., 2014); however, consistent with a direct effect of GLP-2 in islets, GLP-2R mRNA transcripts were detected by real-time polymerase chain reaction (PCR), and GLP-2R immunoreactivity was detected in both rat and human pancreatic α cells (De Heer et al., 2007). On the other hand, in healthy men, GLP-2 administration led to a marked increase in glucagon concentrations both in the fasting state and during the meal study (Meier et al., 2006). Indeed, in obese subjects an inverse relationship between the GLP-2 secretion and insulin sensitivity was reported (Geloneze et al., 2013). In addition, GLP-2 seems also to have an influence on lipids, as it has been shown to cause the release of chylomicrons (and therefore apoB-48 and lipids) in healthy men (Dash et al., 2014). However, the contribution of endogenous GLP-2 to explaining the variance in postprandial TG excursion has been demonstrated to be minor (Matikainen et al., 2016). A study carried out in type 2 diabetic subjects involving intravenous glucose infusion (IIGI) isoglycemic to the excursions after an OGTT plus a concomitant intravenous GLP-2 infusion elicited glucagon responses in the midrange between IIGI alone and the oral glucose tolerance test, thus suggesting that GLP-2 may play a role, even if not predominant, in the inappropriate glucagon response to orally ingested glucose in T2D (Lund et al., 2011). There was no difference between diabetic and control subjects regarding the basal values of GLP-2 in a cohort of postmenopausal women with osteopenia or osteoporosis. GLP-2 levels varied throughout the mixed meal tolerance test in both groups, increasing from baseline to time-point 30 minutes. However, intergroup comparison of response curves showed that the GLP-2 dynamics were similar in both groups throughout the test (Lopes et al., 2015).

Peptide YY

The gut hormone peptide YY (PYY) belongs to the neuropeptide Y (NPY) family along with pancreatic polypeptide (PPY) (Larhammar 1996). PYY, PPY and NPY mediate their effects through Y receptors, of which there are several types (Y1, Y2, Y4, and Y5) (Herzog et al., 2003). Peptide YY (PYY) is released from at least most of the L-cells of the gut, following food intake and appears to regulate intestinal function and possibly also glucose homeostasis, but the extent and the mechanisms underlying these effects are unclear (Cox et al., 2010). Peptide YY (PYY) may be expressed in the α-cells of the islet at certain developmental periods, but its role in control of islet function including insulin secretion is not clear (Shi et al., 2015). Peptide YY (PYY) is best known for its important role in appetite regulation, but recent pharmacological studies have suggested that PYY is also involved in regulating energy balance and glucose homeostasis. Published reports have suggested that low circulating PYY concentrations may causally contribute to the development of hyperinsulinaemia and obesity. In mice on a normal diet, PYY knock-out significantly increased bodyweight, fat mass (Batterham et al., 2003; Boey et al., 2006) and basal and glucose-induced serum insulin levels (Batterham et al., 2003). On the other hand, up-regulation of PYY in islet β-cells leads to an increase in serum insulin levels as well as improved glucose tolerance (Shi et al., 2015). Interestingly, PYY-overproducing mice show increased lean mass and reduced fat mass with no significant changes in food intake or body weight. Energy expenditure is also increased accompanied by increased respiratory exchange ratio (Shi et al., 2015). Interestingly, food composition seems to influence PYY release from the enteroendocrine L cells since either fatty acids (Forbes et al., 2015; Psichas et al., 2015) or aminoacids (Joshi et al., 2013) have been shown to elicit PYY release. Free fatty acid receptor

2 (FFA2) has been demonstrated to be a mediator of release of glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) when activated by short-chain fatty acids (SCFAs). For instance, propionate did not significantly stimulate gut hormone release in FFA2(-/-) mice (Psichas et al., 2015). Furthermore, glutamine stimulates the co-release of endogenous GLP-1 and PYY from mucosal L-cells possibly by activating a calcium-sensing receptor mediated mechanism (Joshi et al., 2013). Following both gastric bypass and sleeve gastrectomy, a significant meal-induced increase in PYY and GLP-1 could be demonstrated (Eickhoff et al., 2015) contributing to improvement in overall glycemic control in lean diabetic rodents. Studies carried out in humans suggest that peptide YY might be involved in the regulation of food intake. In fact, administration of peptide YY active form, i.e. peptide YY 3-36, together with GLP-1 has been shown to reduce total energy intake and fullness at meal onset (Steinert et al., 2010). Also, another study reported that postprandial changes in PYY (area under the curve) were positively associated with postprandial changes in ratings of satiety (Guo et al., 2006). Peptide YY seems not to have a direct and significant influence on insulin and glucose levels as demonstrated by studies which have tested the infusion of PYY in healthy subjects (Ahren et al., 1996; Adrian et al., 1986; Batterham et al., 2003). However, in T2D, it has also been reported that fasting PYY 3-36 levels are significantly higher than controls (English et al., 2006; Ukkola et al., 2011); on the other hand, peptide YY significantly increased postprandially or after oral lipid emulsion administration in normal subjects but did not rise in patients with T2D (English et al., 2006; Fernandez-Garcia et al., 2014). Also, high fasting peptide YY levels have been found to be associated with high body mass index, hemoglobin A1c, glycemia, serum insulin and with higher prevalence of diabetes (Ukkola et al., 2011).

Somatostatin

Somatostatin (SST) derived from islet delta cells exerts a tonic inhibitory influence on insulin and glucagon secretion, which may facilitate the islet response to cholinergic activation because acetyl choline inhibits SST secretion (Holst et al., 1983). In addition, delta-cell SST is implicated in the nutrient-induced suppression of glucagon secretion (Hauge-Evans et al., 2009). The inhibitory effect of SST (SST) on insulin secretion in vivo is attributed to a direct effect on pancreatic beta cells, but this is inconsistent with some in vitro results in which exogenous SST is ineffective in inhibiting secretion from isolated islets. SST does not suppress insulin secretion by a centrally mediated effect but acts peripherally on islet cells (Hauge-Evans et al., 2015). SST inhibition of glucagon release in mouse islets is primarily mediated via SSTR2, one of the 5 somatstatin receptor subtypes, whereas insulin secretion may be regulated primarily via SSTR5, although all of the SST receptors may inhibit insulin secretion (Strowski et al., 2000). SST appears to inhibit adenylate cyclase activity via the inhibitory G-protein G_i but may activate potassium permeability, thereby reducing accumulation of intracellular Ca2+, disrupting glucose-induced stimulus-secretion coupling (Pace et al., 1981). Thus SST induces hyperpolarization and a decrease in the incidence of spike activity, which may prevent glucose from eliciting a normal secretory response (Pace et al., 1977) by inhibiting the rise in [Ca2+]i in pancreatic β-cells (Ma et al., 1996). A basic defect in the glucose sensing of the SST cell in diabetes has not been found yet (Trimble et al., 1981). Contradictory results about SST's role in gastric emptying have been reported in healthy subjects, as both increasing, delaying and neutral effects have been described (Long et al., 1982; Foxx-Orenstein et al., 2003; Jonderko et al., 1989). Regarding satiety, in humans, SST analogues have been found to decrease the sensation

of fullness after a satiating meal (Foxx-Orenstein et al., 2003), but other authors found evidence for a satiety effect of SST (Lieverese et al., 1995). In healthy subjects, SST suppresses plasma growth hormone, glucagon, and insulin leading to an increase in plasma glucose (Christensen et al., 1978). Also, SST has been shown to abolish the responses of glucagon and insulin to an alimentary stimulus, causing an early decrease of plasma glucose followed by a hyperglycemic phase (Marco et al., 1983). Similarly, in T2D, SST suppresses plasma insulin and glucagon (Ward et al., 1977). Continuous infusion of SST has been demonstrated to cause a late-rise of plasma glucose despite continuing hypoglucagonemia (Tamborlane et al., 1977). In patients with T2D, basal levels of SST have been reported to be higher than (Miyazaki et al., 1986) or equal to (D'Alessio et al., 1990) those of healthy subjects. In healthy subjects, SST -like immunoreactivity has been shown to increase after meal or oral administration of glucose, whereas lesser or absent increase of the hormone has been described in subjects with T2D (Miyazaki et al., 1986; Itoh et al., 1983; Gutniak et al., 1989; Grill et al., 1984). In addition, in human type 2 diabetic islets the SST receptor subtype composition differed from that of the controls in SST, pancreatic polypeptide, and glucagon cells (Portela-Gomes et al. 2010).

Serotonin

Over 90% of circulating serotonin or 5-hydroxytriptamine (5-HT) is produced by intestinal enterochromaffin cells (ECs), and as detailed further on, 5-HT modulates bowel motor and secretory activities (Julio-Pieper et al. 2012).

5-HT has been demonstrated to induce a dose-related increase of plasma glucagon after administration to overnight fasted rats, while a blood glucose and insulin increase has been

observed as early as 10 min post-injection in a non-dose-related manner. These results suggest that the 5HT-induced changes in blood glucose and insulin possibly may be secondary to a release of epinephrine and/or norepinephrine (Jacoby et al., 1978). Further, hypothalamic 5HT1A receptors appear to play an important role in the regulation of satiety, glycemia and endocrine status. A 5HT1A agonist (8-OH-DPAT) administered centrally and peripherally to C57/Bl6 mice elicited a dose and time dependent increases in glucose and corticosterone without insulin level variation; further, intracerebroventricular co-administration of a 5HT1A receptor antagonist LY439934 with 5HT1A receptor agonist 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) prevented the increase in plasma glucose, establishing this response as a centrally-mediated response in mice (Gehlert et al., 2014). Therefore, 5HT1A receptors regulate glucose through brain mechanisms, but not through regulation of the hypothalamic-pituitary axis, while antagonism of brain 5HT1A receptors may be molecular targets of novel antidiabetic agents. RT-PCR analysis demonstrated specific expression of 5HT-4 receptors in muscle, but not in the liver or fat tissues (Ueno et al., 2002). A 5HT-4 receptor agonist (Mosapride) has been shown to lower fasting blood glucose and fructosamine concentrations, possibly by increasing glucotransporter GLUT4 recruitment in plasma membrane from intracellular pool (Nam et al., 2010). In humans, contradictory results exist regarding the role of 5-HT in regulating food intake. Depletion of the 5-HT precursor, i.e. tryptophan, has been associated with an increase in caloric intake (Weltzin et al., 1995). However, in a study assessing 192 subjects, those with greater BMI levels showed significantly elevated levels of 5-HIAA, the primary 5-HT metabolite, in cerebrospinal fluid compared to the levels of subjects with lower values (Markianos et al., 2013). On the other hand, the administration of 5-HT agonists, like dexfenfluramine, fenfluramine and lorcaserin, is

associated with reduced weight (Guy-Grand et al., 1989; Weintraub et al., 1992; Fidler et al., 2011). As far as glycemic metabolism is concerned, although in healthy individuals no significant variation has been reported in fasting plasma glucose or insulin after dexfenfluramine administration (Glaser et al., 1992), in patients with T2D treatment with fenfluramine and dexfenfluramine increased insulin sensitivity, reduced hepatic glucose production and decreased visceral fat mass (Pestell et al., 1989; Stewart et al., 1993; Proietto et al., 1994; Marks et al., 1996; Scheen et al., 1991). Similarly, mosapride, a 5HT-4 receptor agonist, has been shown to improve glycemic control and insulin levels in patients with T2D and impaired glucose tolerance (Ueno et al., 2002; Nam et al., 2010). Conversely, 5-HT receptor antagonists, like metergoline and methysergide, seem to have hyperglycemic properties (Wozniak et al., 1991). Involvement of 5-HT in the neurobiology of diabetes has been demonstrated by the detection of significantly greater 5-HT(1A) receptor binding in mesial temporal cortex, including hippocampus of subjects with T2D compared to controls (Price et al., 2002). In addition, a positive correlation between plasma 5-HIAA concentration and changes in urinary albumin excretion was found in T2D, thus possibly indicating a relationship with nephropathy in male patients with T2D mellitus and high plasma 5-HIAA concentration (Fukui et al., 2009). In addition, polymorphisms of 5-HT receptors and transporters have been found to be associated with T2D (Kring et al., 2009; Iordanidou et al., 2010). Furthermore, some investigators reported that 5-HT inhibits insulin and glucagon secretion in human non-diabetic islets in vitro and that this inhibition of insulin release, mediated by 5-HT, is lost in human T2D islets, thus suggesting that loss of inhibition of insulin secretion by 5-HT, as evident in T2D islets, may either contribute to islet dysfunction in T2D or occur as a consequence of already dysfunctional islets (Bennet et al., 2015).

Bile acids

bile acids are secreted into the intestine from the gall bladder in response to a meal and acutely activate intestinal farnesoid X receptor (FXR). In mice with diet-induced obesity and targeted genetic disruption of FXR, subjected to vertical sleeve gastrectomy surgery the ability of bariatric surgery to reduce body weight and improve glucose tolerance was substantially reduced. These data suggest that bile acids and FXR signalling should be considered important molecular underpinnings for the beneficial effects of this type of weight-loss surgery. Treatment of diet-induced obese mice with FXR agonist has been shown to induce a better metabolic profile that includes reduced weight gain, decreased inflammation, browning of WAT and increased insulin sensitization (Fang et al., 2015).

Increased fasting serum levels of 7α-hydroxy-4-cholesten-3-one were found in patients with metabolic syndrome and T2D compared to controls without T2D or metabolic syndrome (Steiner et al., 2011). Moreover, subjects with T2Dcompared to normoglycaemic individuals have been shown to have a higher post-prandial peak change in total bile acids and peak total glycine conjugated bile acids, but similar peak levels of total taurine conjugated bile acids (Vincent et al., 2013), indicating a role of the composition of bile acids in glucose metabolism regulation. Thus, the beneficial effects of FXR agonism bile suggests intestinal FXR therapy as a promising approach in the treatment of insulin resistance and T2D.

Conclusions

T2D is one of the human diseases with the more severe, short and long-term, influence on human health and with a dramatic impact on social and economic aspects of lifestyle. The gut could represent a potential player in the treatment of T2D. In fact, by selectively stimulating the growth of beneficial bacteria in the gut, it has been shown unequivocally to benefit glucose metabolism. Furthermore, prebiotics and probiotics that are usually used to modify the intestinal microbiota are free from the side effects associated with many traditional drug therapies, along with a reasonable cost, thus they could be use on large scale for prevention and/or treatment of T2D. On the other side several gut hormones have been shown to have insulinotropic properties and may be important for normal insulin secretion, particularly after meal ingestion. Since blunted insulin secretion is a main cause of T2D, the gut hormones having insulinotropic property are considered as the promising future therapy of T2D.

Disclosure Statement

The authors have nothing to disclose.

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Table 1. Summary of the gastrointestinal hormones acting on glucose metabolism.

	Source	Food intake	Gastric emptying speed	Insulin secretion	Glucagone secretion	Beta-cell mass	HbA1c
CCK	I-cells	↓	↓	↑	?	↑	↓
Gastrin	Gastric parietal cells	↓	?	↑	?	↑	↓
Ghrelin	Stomach	↑	-	↓	?	↑?	↑?
GIP	K-cells	-	?	↑	↑	-/↑	-
GLP-1	L-cells	↓	↓	↑	↓	↑	↓
GLP-2	L-cells	?	↓	-	↑	?	?
PYY	L-cells	↓	?	↑	?	?	?
Somatostatin	Gastric and Intestinal delta cells	?	↓/↑?	↓	↓	?	?
Serotonin	Intestinal enterochromaffin cells	↓?	?	↓	?	?	↓?
Bile acids	Gall bladder	-	?	?	?	?	↓?

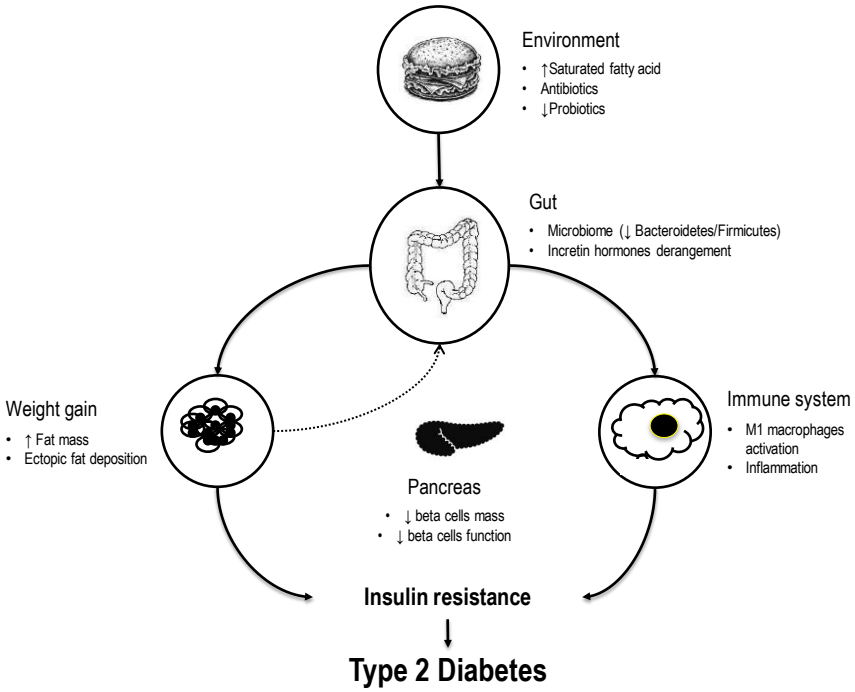

Figure 1