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

Giovanna Muscogiuri, Giancarlo Balercia, Luigi Barrea, Angelo Cignarelli, Francesco Giorgino, Jens J. Holst, Daniela Laudisio, Francesco Orio, Giacomo Tirabassi & Annamaria Colao

Taylor & Francis
Taylor & Francis Group

Check for updates

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

Giovanna Muscogiuri [iD][a], Giancarlo Balercia[b], Luigi Barrea[a], Angelo Cignarelli[c], Francesco Giorgino[c], Jens J. Holst[d], Daniela Laudisio[a], Francesco Orio[e], Giacomo Tirabassi[b], and Annamaria Colao[f]

[a]I.O.S. & COLEMAN Srl, Naples, Italy; [b]Division of Endocrinology, Department of Clinical and Molecular Sciences, Umberto I Hospital, Polytechnic University of Marche, Ancona, Italy; [c]Department of Emergency and Organ Transplantation, Section of Internal Medicine, Endocrinology, Andrology, and Metabolic Diseases, University of Bari Aldo Moro, Bari, Italy; [d]NNF Center for Basic Metabolic Research and Department of Biomedical Sciences, Panum Institute, University of Copenhagen, Copenhagen, Denmark; [e]Endocrinology, Department of Sports Science and Wellness, "Parthenope" University Naples, Naples, Italy; [f]Department of Clinical Medicine and Surgery, "Federico II" University of Naples, Naples, Italy

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 paper 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.

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 et 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 et 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 T2D 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 β cells resulting in "GLP-1 resistance." Thus, the diabetic β cells display a resistance to physiological levels of endogenous GLP-1 (Hojberg et al., 2009). Moreover, a relevant number of T2D subjects exhibit a normal GLP-1 secretion, particularly after an oral glucose tolerance test (OGTT), despite an impaired insulin secretion, suggesting resistance to GLP-1 in human (Knop et al., 2007; Bagger et al., 2011). Additional studies in T2D 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.

T2D 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 (Sekhar and Unnikrishnan, 2015; Egshatyan et al., 2016).

T2Ds 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 nondiabetic 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, 2009; Hildebrandt et al., 2009; Fleissner et al., 2010). 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 β, 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 nondiabetic individuals (Karlsson et al., 2013b). 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
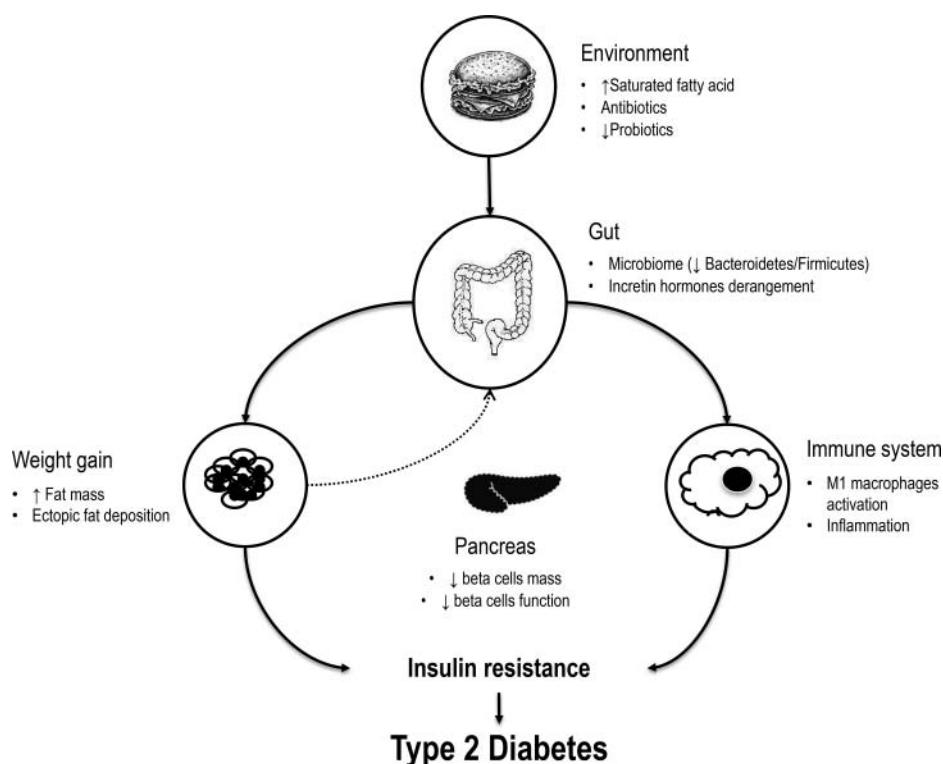

Figure 1. Gut microbiota is crucial in understanding the pathophysiology of several metabolic diseases including that of T2D (Figure 1). The gut microbiota play an important role in the onset of type 2 diabetes by influencing proinflammatory activity, body weight, NAFLD and insulin resistance.NAFLD: Non-alcoholic fatty liver disease.

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 nondiabetic 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 amino acids. *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. (2012) 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. 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., 2013a, 2013b; 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, whereas 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 β-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 (SST)-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 and not 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 appetite regulation. Selective agonists of CCK receptor have been shown to significantly reduce glycated hemoglobin and food intake in a high-fat (HF) fed mouse model (Irwin et al., 2013) especially when coadministered 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 upregulated gene in obese pancreatic islets (Lavine et al., 2010). Interestingly, β-cell proliferation, upregulation 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

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

	Source	Food intake	Gastric emptying speed	Insulin secretion	Glucagone secretion	β-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	—	?	?	?	?	↓?

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 T2D 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 (Suarez-Pinzon et al., 2008; Tellez et al. 2011, 2014; Sasaki et al., 2015). The effects of treatment with gastrin on β-cell appear even more pronounced when combined with either GLP-1R agonists (Suarez-Pinzon et al., 2008; Fosgerau et al., 2013) 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 β-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-week, 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 (Mefford et al., 2012; Inci et al., 2014). A study evaluating patients with T2Ds 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 T2Ds 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 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, 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 10 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). However, in T2D 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 T2D patients before insulin therapy compared to nondiabetic patients (Anderwald et al., 2003).

Glucose-dependent insulinotropic peptide

Enteroendocrine K cells secrete the incretin hormone glucose-dependent insulinotropic peptide (GIP), and are predominately located in the duodenum and the proximal small intestine. GIP is a peptide hormone which potentiates glucose-stimulated insulin secretion during a meal. Although 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 and Seino, 2011). GIP has the potential to ameliorate glucose intolerance even after STZ-induced β-cell damage by increasing insulin secretion rather than by promoting β-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 hyperglycemia), 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 HF fed mice (Hinke et al. 2002; Gault et al., 2011; Kim et al., 2012). In addition, subcutaneous administration of D-Ala2-GIP1-30 to Zucker diabetic fatty rats had potent antidiabetic 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, 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 HF 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, 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 (Irwin and Flatt, 2009; Gniuli et al., 2010). 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 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 (Sarson et al., 1984; Meier et al., 2004; Asmar et al., 2010). 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 nondiabetic subjects, thus indicating an impaired GIP secretion and effect in T2D (Groop et al., 1985; Skrha et al., 2010).

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 HF 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 (Lavine et al., 2010; Bagger et al., 2011; 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 HF foods (Williams et al., 2011). GLP-1 and its analogs may preserve pancreatic β-cell mass by promoting resistance to cytokine-mediated apoptosis (Natalicchio et al., 2010, 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. In addition, 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 β cells in experimental diabetes models (Li et al., 2003). In an earlier study, Ling et al. (2001) showed that GLP-1 receptor (GLP-1R) KO mice display normal β-cell mass. However, β-cell recovery after partial pancreatectomy appear reduced in GLP-1R KO 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 KO mice) resulted in impairment of β-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., 2012; Vella, 2013). Noteworthy, in nonobese 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 HF 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 consecutive 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 (Willms et al., 1996; Nauck et al., 1997; Wettergren et al., 2010). 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, 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 (Legakis et al., 2003; Lastya et al., 2014) or equal (Lee et al., 2010) than those of healthy subjects. However, the meal-related glucagon-like 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 OGTT (Bagger et al., 2011; Faerch et al., 2015).

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 (Schmidt et al., 1985; Orskov et al., 1988). 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 SDT 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 and Amato, 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). However, 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 T2D 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 OGTT, 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, 2003). 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). 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). 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 hyperinsulinemia and obesity. In mice on a normal diet, PYY KO significantly increased body-weight, fat mass (Batterham et al., 2003; Boey et al., 2006) and basal and glucose-induced serum insulin levels (Batterham et al., 2003). However, upregulation 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 because either fatty acids (Forbes et al., 2015; Psichas et al., 2015) or amino acids (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 corelease 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 PYY might be involved in the regulation of food intake. In fact, administration of PYY active form, i.e. PYY 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). PYY 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 (Adrian et al., 1986; Ahren and Larsson, 1996; 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); however, 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

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 β 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 five 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 Ca^{2+}, disrupting glucose-induced stimulus-secretion coupling (Pace and Tarvin, 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 $[Ca^{2+}]_i$ 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; Jonderko et al., 1989; Foxx-Orenstein et al., 2003). 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 (Itoh et al., 1983; Grill et al., 1984; Miyazaki et al., 1986; Gutniak et al., 1989). In addition, in human T2D 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

More than 90% of circulating serotonin or 5-hydroxytryptamine (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, whereas a blood glucose and insulin increase has been observed as early as 10-minute 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 and Bryce, 1978). Furthermore, 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; furthermore, 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 and Shaw, 2014). Therefore, 5HT1A receptors regulate glucose through brain mechanisms, but not through regulation of the hypothalamic–pituitary axis, whereas 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). However, 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; Scheen et al., 1991; Stewart et al., 1993; Proietto et al., 1994; Marks et al., 1996). 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 and Linnoila, 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 nondiabetic 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 T2D compared to normoglycaemic individuals have been shown to have a higher postprandial 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 used on large scale for prevention and/or treatment of T2D. However, several gut hormones have been shown to have insulinotropic properties and may be important for normal insulin secretion, particularly after meal ingestion. Because 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

ORCID

Giovanna Muscogiuri http://orcid.org/0000-0002-8809-4931

References

Adrian, T. E., Sagor, G. R., Savage, A. P., Bacarese-Hamilton, A. J., Hall, G. M. and Bloom, S. R. (1986). Peptide YY kinetics and effects on blood pressure and circulating pancreatic and gastrointestinal hormones and metabolites in man. *J. Clin. Endocrinol Metab.* **63**(4):803–807.

Ahren, B. and Larsson, H.(1996). Peptide YY does not inhibit glucose-stimulated insulin secretion in humans. *Eur. J. Endocrinol.* **134**(3):362–365.

Ahrén, B., Holst, J. J. and Efendic, S. (2000). Antidiabetogenic action of cholecystokinin-8 in type 2 diabetes. *J. Clin. Endocrinol. Metab.* **85**(3):1043–1048.

Althage, M. C., Ford, E. L., Wang, S., Tso, P., Polonsky, K. S., and Wice, B. M. (2008). Targeted ablation of glucose-dependent insulinotropic polypeptide-producing cells in transgenic mice reduces obesity and insulin resistance induced by a high fat diet. *J. Biol. Chem.* **283**(26):18365–18376.

Amini, P., Wadden, D., Cahill, F., Randell, E., Vasdev, S., Chen, X., Gulliver, W., Zhang, W., Zhang, H., Yi, Y. and Sun, G. (2012). Serum acylated ghrelin is negatively correlated with the insulin resistance in the CODING study. *Plos One* **7**(9):e45657.

Anderwald, C., Brabant, G., Bernroider, E., Horn, R., Brehm, A., Waldhäusl, W. and Roden, M. (2003). Insulin-dependent modulation of plasma ghrelin and leptin concentrations is less pronounced in type 2 diabetic patients. *Diabetes.* **52**(7):1792–1798.

Anini, Y. and Brubaker, P. L. (2003). Role of leptin in the regulation of glucagon-like peptide-1 secretion. *Diabetes.* **52**(2):252–259.

Asmar, M., Tangaa, W., Madsbad, S., Hare, K., Astrup, A., Flint, A., Bülow, J. and Holst, J.J. (2010). On the role of glucose-dependent insulintropic polypeptide in postprandial metabolism in humans. *Am. J. Physiol. Endocrinol. Metab.* **298**(3):E614–E621.

Backhed, F., Ding, H., Wang, T., Hooper, L. V., Koh, G. Y., Nagy, A., Semenkovich, C. F. and Gordon, J. I. (2004). The gut microbiota as an environmental factor that regulates fat storage. *Proc. Natl. Acad. Sci. U S A.* **101**(44):15718–15723.

Bagger, J. I., Knop, F. K., Lund, A., Vestergaard, H., Holst, J. J. and Vilsboll, T. (2011). Impaired regulation of the incretin effect in patients with type 2 diabetes. *J. Clin. Endocrinol. Metab.* **96**:737–745.

Bahrami, J., Longuet, C., Baggio, L. L., Li, K. and Drucker, D. J. (2010). Glucagon-like peptide-2 receptor modulates islet adaptation to metabolic stress in the ob/ob mouse. *Gastroenterology*, **96**(3):737–745.

Baldassano, S. and Amato, A. (2014). GLP-2: What do we know? What are we going to discover?. *Regul. Peptides* **194–195**:6–10.

Batterham, R. L., Cohen, M. A., Ellis, S. M., Le Roux, C. W., Withers, D. J., Frost, G. S. and Bloom, S. R. (2003). Inhibition of food intake in obese subjects by peptide YY 3–36. *New Engl. J. Med.*, **349**(10):941–948.

Bennet, H., Balhuizen, A., Medina, A., Dekker Nitert, M., Ottosson Laakso, E., Essén, S., Spégel, P., Storm, P., Krus, U., Wierup, N. and Fex, M. (2015). Altered serotonin (5-HT) 1D and 2A receptor expression may contribute to defective insulin and glucagon secretion in human type 2 diabetes. *Peptides.* **71**:113–120.

Boey, D., Lin, S., Karl, T., Baldock, P., Lee, N., Enriquez, R. and Herzog, H. (2006). Peptide YY ablation in mice leads to the development of hyperinsulinaemia and obesity. *Diabetologia.* **49**(6):1360–1370.

Breen, D. M., Rasmussen, B. A., Côté, C. D., Jackson, V. M. and Lam, T. K. (2013). Nutrient-sensing mechanisms in the gut as therapeutic targets for diabetes. *Diabetes.* **62**(9):3005–3013.

Broglio, F., Arvat, E., Benso, A., Gottero, C., Muccioli, G., Papotti, M., van der Lely, A. J., Deghenghi, R. and Ghigo, E. (2001). Ghrelin, a natural GH secretagogue produced by the stomach, induces hyperglycemia and reduces insulin secretion in humans. *J. Clin. Endocrinol. Metab.* **86**(10):5083–5086.

Broglio, F., Prodam, F., Riganti, F., Gottero, C., Destefanis, S., Granata, R., Muccioli, G., Abribat, T., van der Lely, A. J. and Ghigo, E. (2008). The continuous infusion of acylated ghrelin enhances growth hormone secretion and worsens glucose metabolism in humans. *J. Endocrinol. Invest.* **31**(9):788–794.

Broussard, J. L., Kilkus, J. M., Delebecque, F., Abraham, V., Day, A., Whitmore, H. R. and Tasali, E. (2016). Elevated ghrelin predicts food intake during experimental sleep restriction. *Obesity (Silver Spring).* **24**(1):132–138.

Bulotta, A., Farilla, L., Hui, H. and Perfetti, R. (2004). The role of GLP-1 in the regulation of islet cell mass. *Cell Biochem. Biophys.* **40**(3):65–78.

Burcelin, R., Serino, M., Chabo, C., Blasco-Baque, V. and Amar, J. (2011). Gut microbiota and diabetes: From pathogenesis to therapeutic perspective. *Acta Diabetol.* **48**:257–273.

Camilleri, M., Papathanasopoulos, A. and Odunsi, S. T. (2009). Actions and therapeutic pathways of ghrelin for gastrointestinal disorders. *Nat. Rev. Gastroenterol. Hepatol.* **6**(6):343–352.

Cani, P. D., Geurts, L., Matamoros, S., Plovier, H. and Duparc, T. (2014). Glucose metabolism: Focus on gut microbiota, the endocannabinoid system and beyond. *Diab. Metab.* **40**(4):246–257.

Chia, C. W., Carlson, O. D., Kim, W., Shin, Y. K., Charles, C. P., Kim, H. S., Melvin, D. L. and Egan, J. M. (2009). Exogenous glucose-dependent insulinotropic polypeptide worsens post prandial hyperglycemia in type 2 diabetes. *Diabetes.* **58**(6):1342–1349.

Christensen, M., Calanna, S., Sparre-Ulrich, A. H., Kristensen, P. L., Rosenkilde, M. M., Faber, J., Purrello, F., Van Hall, G., Holst, J. J., Vilsbøll, T., Knop, F. K. (2015). Glucose-dependent insulinotropic polypeptide augments glucagon responses to hypoglycemia in type 1 diabetes. *Diabetes.* **64**(1):72–78.

Christensen, S. E., Hansen, A. P., Weeke, J. and Lundbaek, K. (1978). 24-hour studies of the effects of somatostatin on the levels of plasma growth hormone, glucagon, and glucose in normal subjects and juvenile diabetics. *Diabetes.* **27**(3):300–306.

Cox, H. M., Tough, I. R., Woolston, A.-M., Zhang, L., Nguyen, A. D., Sainsbury, A. and Herzog, H. (2010). Peptide YY is critical for acylethanolamine receptor Gpr119-induced activation of gastrointestinal mucosal responses. *Cell Metabolism.* **11**(6):532–542.

Crockett, S. E., Mazzaferri, E. L. and Cataland, S. (1976).Gastric inhibitory polypeptide (GIP) in maturity-onset diabetes mellitus. *Diabetes.* **25**(10):931–935.

Cummings, D. E., Overduin, J., Foster-Schubert, K. E. and Carlson, M. J. (2007). Role of the bypassed proximal intestine in the anti-diabetic effects of bariatric surgery. *Surg. Obesity Relat Diseases.* **3**(2):109–115.

Cummings, D. E., Purnell, J. Q., Frayo, R. S., Schmidova, K., Wisse, B. E. and Weigle, D. S. (2001). A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. *Diabetes.* **50**(8):1714–1749.

D'Alessio, D. A. and Ensinck, J. W. (1990). Fasting and postprandial concentrations of somatostatin-28 and somatostatin-14 in type II diabetes in men. *Diabetes.* **39**(10):1198–1202.

Dash, S., Xiao, C., Morgantini, C., Connelly, P. W., Patterson, B. W. and Lewis, G. F. (2014). Glucagon-like peptide-2 regulates release of chylomicrons from the intestine. *Gastroenterology.* **147**(6):1275–1284.e4.

De Heer, J., Pedersen, J., Orskov, C. and Holst, J. J. (2007). The alpha cell expresses glucagon-like peptide-2 receptors and glucagon-like peptide-2 stimulates glucagon secretion from the rat pancreas. *Diabetologia.* **50**(10):2135–2142.

De Jonghe, B. C., Hajnal, A. and Covasa, M. (2005). Increased oral and decreased intestinal sensitivity to sucrose in obese, prediabetic CCK-A receptor-deficient OLETF rats. *Am. J. Physiol. Regul. Integr. Comparat. Physiol.* **288**(1):R292–R300.

De Leon, D. D., Deng, S., Madani, R., Ahima, R. S., Drucker, D. J. and Stoffers, D. A. (2003). Role of endogenous glucagon-like peptide-1 in islet regeneration after partial pancreatectomy. *Diabetes.* **52**(2):365–371.

De Luis, D., Domingo, M., Romero, A., Gonzalez Sagrado, M., Pacheco, D., Primo, D. and Conde, R. (2012). Effects of duodenal-jejunal exclusion on beta cell function and hormonal regulation in Goto-Kakizaki rats. *Am. J. Surg.*, **204**(2):242–247.

Dirksen, C., Hansen, D. L., Madsbad, S., Hvolris, L. E., Naver, L. S., Holst, J. J. and Worm, D. (2010). Postprandial diabetic glucose tolerance is normalized by gastric bypass feeding as opposed to gastric feeding and is associated with exaggerated GLP-1 secretion: A case report. *Diabetes Care.* **33**:375–377.

Dupre, J., Curtis, J.D., Unger, R.H., Waddell, R. W. and Beck, J. C. (1969). Effects of secretin, pancreozymin, or gastrin on the response of the endocrine pancreas to administration of glucose or arginine in man. *Clin. Invest.* **48**(4):745–757.

Edholm, T., Degerblad, M., Grybäck, P., Hilsted, L., Holst, J. J., Jacobsson, H., Efendic, S., Schmidt, P. T. and Hellström, P. M. (2010). Differential incretin effects of GIP and GLP-1 on gastric emptying, appetite, and insulin-glucose homeostasis. *Neurogastroenterol Motil.* **22**(11):1191–1200.

Egshatyan, L., Kashtanova, D., Popenko, A., Tkacheva, O., Tyakht, A., Alexeev, D., Karamnova, N., Kostryukova, E., Babenko, V., Vakhitova, M. and Boytsov, S. (2016). Gut microbiota and diet in patients with different glucose tolerance. *Endocr. Connect.* **5**(1):1–9.

Eickhoff, H., Louro, T. M., Matafome, P. N., Vasconcelos, F., Seiça, R. M., Castro, E. and Sousa, F. (2015). Amelioration of glycemic control by sleeve gastrectomy and gastric bypass in a lean animal model of type 2 diabetes: Restoration of gut hormone profile. *Obes. Surg.* **25**(1):7–18.

English, P. J., Ashcroft, A., Patterson, M., Dovey, T. M., Halford, J. C., Harrison, J., Eccleston, D., Bloom, S. R., Ghatei, M. A. and Wilding, J. P. (2006).Fasting plasma peptide-YY concentrations are elevated but do not rise postprandially in type 2 diabetes. *Diabetologia.* **49**(9):2219–2221.

Erdmann, J., Lippl, F., Wagenpfeil, S. and Schusdziarra, V. (2005). Differential association of basal and postprandial plasma ghrelin with leptin, insulin, and type 2 diabetes. *Diabetes.* **54**(5):1371–1378.

Faerch, K., Torekov, S. S., Vistisen, D., Johansen, N. B., Witte, D. R., Jonsson, A., Pedersen, O., Hansen, T., Lauritzen, T., Sandbæk, A., Holst, J. J., Jørgensen, M. E. (2015).GLP-1 response to oral glucose is reduced in prediabetes, screen-detected type 2 diabetes, and obesity and influenced by sex: The ADDITION-PRO study. *Diabetes.* **64**(7):2513–2325.

Fang, S., Suh, J. M., Reilly, S. M., Yu, E., Osborn, O., Lackey, D., Yoshihara, E., Perino, A., Jacinto, S., Lukasheva, Y., Atkins, A. R., Khvat, A., Schnabl, B., Yu, R. T., Brenner, D. A., Coulter, S., Liddle, C., Schoonjans, K., Olefsky, J. M., Saltiel, A. R., Downes, M. and Evans, R. M. (2015). Intestinal FXR agonism promotes adipose tissue browning and reduces obesity and insulin resistance. *Nat. Med.* **21**(2):159–165.

Farilla, L., Hui, H., Bertolotto, C., Kang, E., Bulotta, A., Di Mario, U. and Perfetti, R. (2002). Glucagon-like peptide-1 promotes islet cell growth and inhibits apoptosis in Zucker diabetic rats. *Endocrinology.* **143**(11):4397–4408.

Fernández-García, J. C., Murri, M., Coin-Aragüez, L., Alcaide, J., El Bekay, R. and Tinahones, F. J. (2014).GLP-1 and peptide YY secretory response after fat load is impaired by insulin resistance, impaired fasting glucose and type 2 diabetes in morbidly obese subjects. *Clin. Endocrinol (Oxf).* **80**(5):671–676.

Fidler, M. C., Sanchez, M., Raether, B., Weissman, N. J., Smith, S. R., Shanahan, W. R. and Anderson, C. M. (2011). BLOSSOM Clinical Trial Group.A one-year randomized trial of lorcaserin for weight loss in obese and overweight adults: The BLOSSOM trial. *J. Clin. Endocrinol. Metab.* **96**(10):3067–3077.

Fleissner, C.K., Huebel, N., Abd El-Bary, M.M., Loh, G., Klaus, S., and Blaut, M. (2010). Absence of intestinal microbiota does not protect mice from dietinduced obesity. *Br. J. Nutr.* **104**:919–929.

Flint, A., Raben, A., Astrup, A. and Holst, J. J. (1998). Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. *J. Clin. Invest.* **101**(3):515–520.

Forbes, S., Stafford, S., Coope, G., Heffron, H., Real, K., Newman, R. and Cox, H. (2015). Selective FFA2 agonism appears to act via intestinal PYY to reduce transit and food intake but does not improve glucose tolerance in mouse models. *Diabetes.* **64**(11):3763–3771.

Fosgerau, K., Jessen, L., Lind Tolborg, J., Østerlund, T., Schæffer Larsen, K., Rolsted, K. and Skovlund Ryge Neerup, T. (2013). The novel GLP-1-gastrin dual agonist, ZP3022, increases β-cell mass and prevents diabetes in db/db mice. *Diab. Obes. Metab.* **15**(1):62–71.

Foxx-Orenstein, A., Camilleri, M., Stephens, D. and Burton, D. (2003). Effect of a somatostatin analogue on gastric motor and sensory functions in healthy humans. *Gut.* **52**(11):1555–1561.

Fukui, M., Shiraishi, E., Tanaka, M., Senmaru, T., Sakabe, K., Harusato, I., Hasegawa, G. and Nakamura, N. (2009). Plasma serotonin is a predictor for deterioration of urinary albumin excretion in men with type 2 diabetes mellitus. *Metabolism.* **58**(8):1076–1079.

Fulurija, A., Lutz, T. A., Sladko, K., Osto, M., Wielinga, P. Y., Bachmann, M. F. and Saudan, P. (2008). Vaccination against GIP for the treatment of obesity. *PLoS ONE.* **3**(9):e3163.

Gault, V. A., Porter, D., Irwin, N. and Flatt, P. R. (2011). Comparison of sub-chronic metabolic effects of stable forms of naturally occurring GIP(1–30) and GIP(1–42) in high fat fed mice. *J. Endocrinology.* **208**(3):265–271.

Gauna, C., Delhanty, P. J. D., Hofland, L. J., Janssen, J. A. M. J. L., Broglio, F., Ross, R. J. M. and Van der Lely, A. J. (2005). Ghrelin stimulates, whereas des-octanoyl ghrelin inhibits, glucose output by primary hepatocytes. *J. Clin. Endocrinol. Metab.* **90**(2):1055–1060.

Gehlert, D. R. and Shaw, J. (2014). 5-Hydroxytryptamine 1A (5HT1A) receptors mediate increases in plasma glucose independent of corticosterone. *Eur. J. Pharmacol.* **745**:91–7.

Geloneze, B., Lima, M. M., Pareja, J. C., Barreto, M. R. and Magro, D. O. (2013). Association of insulin resistance and GLP-2 secretion in obesity: A pilot study. *Arq. Bras. Endocrinol. Metabol.* **57**(8):632–635.

Geurts, L., Lazarevic, V., Derrien, M., et al. (2011). Altered gut microbiota and endocannabinoid system tone in obese and diabetic leptin-resistant mice: Impact on apelin regulation in adipose tissue. *Front Microbiol.* **2**:1–17.

Glaser, B., Raveh, Y., Norynberg, C., Berry, E., Lavielle, R., Nathan, C. and Cerasi, E. (1992). Acute and chronic effects of dexfenfluramine on glucose and insulin response to intravenous glucose in diabetic and non-diabetic obese subjects. *Diabetes Res.* **19**(4):165–176.

World Health Organization, Global report on diabetes. World Health Organization, Geneva, 2016.

Gniuli, D., Calcagno, A., Dalla Libera, L., Calvani, R., Leccesi, L., Caristo, M. E. and Mingrone, G. (2010). High-fat feeding stimulates endocrine, glucose-dependent insulinotropic polypeptide (GIP)-expressing cell hyperplasia in the duodenum of Wistar rats. *Diabetologia.* **53**(10):2233–2240.

González-Ortiz, M., Martínez-Abundis, E., Mercado-Sesma, A. R. and Álvarez-Carrillo, R. (2015). Effect of pantoprazole on insulin secretion in drug-naïve patients with type 2 diabetes. *Diabetes Res. Clin. Pract.* **108**(1):e11–e13.

Granata, R., Settanni, F., Biancone, L., Trovato, L., Nano, R., Bertuzzi, F. and Muccioli, G. (2007). Acylated and unacylated ghrelin promote proliferation and inhibit apoptosis of pancreatic beta-cells and human islets: Involvement of 3′,5′-cyclic adenosine monophosphate/protein kinase A, extracellular signal-regulated kinase 1/2, and phosphatidyl inosit. *Endocrinology.* **148**(2):512–529.

Grill, V., Gutniak, M., Roovete, A. and Efendić, S. (1984). A stimulating effect of glucose on somatostatin release is impaired in noninsulin-dependent diabetes mellitus. *J. Clin. Endocrinol. Metab.* **59**(2):293–297.

Groop, P. H., Fyhrquist, F. and Groop, L. C. (1985).Effect of serial test meals on plasma immunoreactive GIP in non-insulin dependent diabetic patients and non-diabetic controls. *Scand. J. Clin. Lab. Invest.* **45**(2):115–22.

Guo, Y., Ma, L., Enriori, P. J., Koska, J., Franks, P. W., Brookshire, T., Cowley, M. A., Salbe, A. D., Delparigi, A. and Tataranni, P. A. (2006). Physiological evidence for the involvement of peptide YY in the regulation of energy homeostasis in humans. *Obesity (Silver Spring).* **14**(9):1562–1570.

Gutniak, M., Grill, V., Roovete, A. and Efendic, S. (1989). Impaired somatostatin response to orally administered glucose in type II diabetes entails both somatostatin-28 and -14 and is associated with deranged metabolic control. *Acta Endocrinol. (Copenh)* **121**(3):322–326.

Gutzwiller, J. P, Drewe, J., Hildebrand, P., Rossi, L., Lauper, J. Z. and Beglinger, C. (1994). Effect of intravenous human gastrin-releasing peptide on food intake in humans. *Gastroenterology.* **106**(5):1168–1173.

Gutzwiller, J. P., Drewe, J., Göke, B., Schmidt, H., Rohrer, B., Lareida, J. and Beglinger, C. (1999). Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. *Am. J. Physiol.* **276**(5 Pt 2):R1541–R1544.

Guy-Grand, B., Apfelbaum, M., Crepaldi, G., Gries, A., Lefebvre, P. and Turner, P. (1989). International trial of long-term dexfenfluramine in obesity. *Lancet.* **2**(8672):1142–1145.

Hauge-Evans, A. C., Bowe, J., Franklin, Z. J., Hassan, Z. and Jones, P. M. (2015). Inhibitory effect of somatostatin on insulin secretion is not mediated via the CNS. *J. Endocrinology.* **225**(1):19–26.

Hauge-Evans, A. C., King, A. J., Carmignac, D., Richardson, C. C., Robinson, I. C. A. F., Low, M. J. and Jones, P. M. (2009). Somatostatin

secreted by islet delta-cells fulfills multiple roles as a paracrine regulator of islet function. *Diabetes.* **58**(2) 403–411.

He, C., Shan, Y. and Song, W.(2015). Targeting gut microbiota as a possible therapy for diabetes. *Nutr. Res.* **35**(5):361–367.

Herzog, H. (2003). Neuropeptide Y and energy homeostasis: Insights from Y receptor knockout models. *Eur. J. Pharmacology.* **480**(1–3):21–29.

Hildebrandt, M. A, Hoffmann, C., Sherrill-Mix, S. A, et al. (2009). High-fat diet determines the composition of the murine gut microbiome independently of obesity. *Gastroenterology.* **137**:1716–1724.e1–2.

Hinke, S. A., Gelling, R. W., Pederson, R. A., Manhart, S., Nian, C., Demuth, H.-U. and McIntosh, C. H. S. (2002). Dipeptidyl peptidase IV-resistant [D-Ala2] glucose-dependent insulinotropic polypeptide (GIP) improves glucose tolerance in normal and obese diabetic rats. *Diabetes.* **51**(3):652–661.

Hojberg, P. V. et al. (2009). Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. *Diabetologia.* **52**:199–207.

Holst, J. J., Jensen, S. L., Knuhtsen, S. and Nielsen, O. V (1983). Autonomic nervous control of pancreatic somatostatin secretion. *Am. J. Physiol.* **245**:E542–E548.

Iida, A., Seino, Y., Fukami, A., Maekawa, R., Yabe, D., Shimizu, S. and Hayashi, Y. (2016). Endogenous GIP ameliorates impairment of insulin secretion in proglucagon-deficient mice under moderate beta cell damage induced by streptozotocin. *Diabetologia.* **59**(7):1533–1541.

Inci, F., Atmaca, M., Ozturk, M., Yildiz, S., Koceroglu, R., Sekeroglu, R., Ipekci, S.H. and Kebapcilar, L. (2014). Pantoprazole may improve beta cell function and diabetes mellitus. *J. Endocrinol Invest.* **37**(5):449–454.

Iordanidou, M., Tavridou, A., Petridis, I., Arvanitidis, K.I., Christakidis, D., Vargemezis, V. and Manolopoulos, V. G. (2010). The serotonin transporter promoter polymorphism (5-HTTLPR) is associated with type 2 diabetes. *Clin. Chim. Acta.* **411**(3–4):167–171.

Irwin, N. and Flatt, P. R. (2009). Evidence for beneficial effects of compromised gastric inhibitory polypeptide action in obesity-related diabetes and possible therapeutic implications. *Diabetologia.* **52**(9):1724–1731.

Irwin, N., Hunter, K., Montgomery, I. A. and Flatt, P. R. (2013a). Comparison of independent and combined metabolic effects of chronic treatment with (pGlu-Gln)-CCK-8 and long-acting GLP-1 and GIP mimetics in high fat-fed mice. *Diabetes, Obesity Metabolism.* **15**(7):650–659.

Irwin, N., Montgomery, I. A., Moffett, R. C. and Flatt, P. R. (2013). Chemical cholecystokinin receptor activation protects against obesity-diabetes in high fat fed mice and has sustainable beneficial effects in genetic ob/ob mice. *Biochem. Pharmacology.* **85**(1):81–91.

Itoh, M., Hirooka, Y. and Nihei, N. (1983). Response of plasma somatostatin-like immunoreactivity (SLI) to a 75 g oral glucose tolerance test in normal subjects and patients with impaired glucose tolerance. *Acta. Endocrinol. (Copenh).* **104**(4):468–474.

Jacoby, J. H. and Bryce, G. F. (1978). The acute pharmacologic effects of serotonin on the release of insulin and glucagon in the intact rat. *Arch. Intl. Pharmacodyn. Thérap.* **235**(2):254–270.

Jonderko, G., Jonderko, K. and Gołab, T. (1989). Effect of somatostatin-14 on gastric emptying and on gastrin and insulin release after ingestion of a mixed solid-liquid meal in man. *Mater. Med. Pol.* **21**(3):174–180.

Jones, I. R., Owens, D. R., Moody, A. J., Luzio, S. D., Morris, T. and Hayes, T. M. (1987). The effects of glucose-dependent insulinotropic polypeptide infused at physiological concentrations in normal subjects and type 2 (non-insulin-dependent) diabetic patients on glucose tolerance and B-cell secretion. *Diabetologia.* **30**(9):707–712.

Joshi, S., Tough, I. R. and Cox, H. M. (2013). Endogenous PYY and GLP-1 mediate l-glutamine responses in intestinal mucosa. *Br. J. Pharmacol.* **170**(5):1092–1101.

Julio-Pieper, M., O'Mahony, C. M., Clarke, G., Bravo, J. A., Dinan, T. G. and Cryan, J. F. (2012). Chronic stress-induced alterations in mouse colonic 5-HT and defecation responses are strain dependent. *Stress.* **15**:218–226.

Kampmann, K., Ueberberg, S., Menge, B. A., Breuer, T. G. K., Uhl, W., Tannapfel, A. and Meier, J. J. (2016). Abundance and turnover of GLP-1 producing L-cells in ileal mucosa are not different in patients with and without type 2 diabetes. *Metab.: Clin. Exp.*, **65**(3):84–91.

Karlsson, F., Tremaroli, V., Nielsen, J. and Bäckhed, F. (2013a). Assessing the human gut microbiota in metabolic diseases. *Diabetes.* **62**(10):3341–3349.

Karlsson, F.H., Tremaroli, V., Nookaew, I., et al. (2013b). Gut metagenome in European women with normal, impaired and diabeteic glucose control. *Nature.* **498**:99–103.

Katsuki, A., Urakawa, H., Gabazza, E.C., Murashima, S., Nakatani, K., Togashi, K., Yano, Y., Adachi, Y. and Sumida, Y. (2004). Circulating levels of active ghrelin is associated with abdominal adiposity, hyperinsulinemia and insulin resistance in patients with type 2 diabetes mellitus. *Eur. J. Endocrinol.* **151**(5):573–577.

Kim, S.-J., Nian, C., Karunakaran, S., Clee, S. M., Isales, C. M. and McIntosh, C. H. S. (2012). GIP-overexpressing mice demonstrate reduced diet-induced obesity and steatosis, and improved glucose homeostasis. *PloS One.* **7**(7):e40156.

Kissileff, H. R., Pi-Sunyer, F. X., Thornton, J. and Smith, G. P. (1981). C-terminal octapeptide of cholecystokinin decreases food intake in man. *Am. J. Clin. Nutr.* **34**(2):154–160.

Knop, F. K., Vilsboll, T., Madsbad, S., Holst, J. J., and Krarup, T. (2007). Inappropriate suppression of glucagon during OGTT but not during isoglycaemic i.v. glucose infusion contributes to the reduced incretin effect in type 2 diabetes mellitus. *Diabetologia.* **50**: 797–805.

Kojima, M. (2005). Ghrelin: Structure and function. *Physiol. Rev.* **85**(2):495–522.

Kootte, R. S, Vrieze, A., Holleman, F., Dallinga-Thie, G. M., Zoetendal, E. G., de Vos, W. M., Groen, A. K., Hoekstra, J. B., Stroes, E. S. and Nieuwdorp, M. (2012).The therapeutic potential of manipulating gut microbiota in obesity and type 2 diabetes mellitus. *Diab. Obes. Metab.* **14**(2):112–120.

Kreymann, B., Williams, G., Ghatei, M. A. and Bloom, S. R. (1987).Glucagon-like peptide-1 7–36: A physiological incretin in man. *Lancet.* **2**(8571):1300–1304.

Kring, S. I., Werge, T., Holst, C., Toubro, S., Astrup, A., Hansen, T., Pedersen, O. and Sorensen, T. I. (2009). Polymorphisms of serotonin receptor 2A and 2C genes and COMT in relation to obesity and type 2 diabetes. *PLoS One.* **4**(8):e6696.

Larhammar, D. (1996). Evolution of neuropeptide Y, peptide YY and pancreatic polypeptide. *Regulatory Peptides.* **62**(1):1–11.

Larsen, N., Vogensen, F. K., van den Berg, F. W., Nielsen, D. S., Andreasen, A. S., Pedersen, B. K., Al-Soud, W. A., Sørensen, S. J., Hansen, L. H. and Jakobsen, M. (2010).Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One.* **5**:e9085.

Lastya, A., Saraswati, M. R. and Suastika, K. (2014). The low level of glucagon-like peptide-1 (glp-1) is a risk factor of type 2 diabetes mellitus. *BMC Res. Notes* **7**:849.

Lavine, J. A., Kibbe, C. R., Baan, M., Sirinvaravong, S., Umhoefer, H. M., Engler, K. A., and Davis, D. B. (2015). Cholecystokinin expression in the β-cell leads to increased β-cell area in aged mice and protects from streptozotocin-induced diabetes and apoptosis. *Am. J. Physiol. Endocrinol. Metab.* **309**(10):E819–E828.

Lavine, J. A., Raess, P. W., Davis, D. B., Rabaglia, M. E., Presley, B. K., Keller, M. P. and Attie, A. D. (2008). Overexpression of pre-pro-cholecystokinin stimulates beta-cell proliferation in mouse and human islets with retention of islet function. *Molec. Endocrinol. (Baltimore, Md.).* **22**(12):2716–2728.

Lavine, J. A., Raess, P. W., Stapleton, D. S., Rabaglia, M. E., Suhonen, J. I., Schueler, K. L., and Attie, A. D. (2010). Cholecystokinin is up-regulated in obese mouse islets and expands beta-cell mass by increasing beta-cell survival. *Endocrinology.* **151**(8):3577–3588.

Le, T. K., Hosaka, T., Nguyen, T. T., Kassu, A., Dang, T. O., Tran, H. B, Pham, T. P., Tran, Q. B., Le, T. H., Pham, X. D. (2015). Bifidobacterium species lower serum glucose, increase expressions of insulin signaling proteins, and improve adipokine profile in diabetic mice. *Biomed. Res.* **36**(1):63–70.

Lee, S., Yabe, D., Nohtomi, K., Takada, M., Morita, R., Seino, Y. and Hirano, T. (2010). Intact glucagon-like peptide-1 levels are not decreased in Japanese patients with type 2 diabetes. *Endocr J.* **57**(2):119–126.

Legakis, I. N., Tzioras, C. and Phenekos, C. (2003). Decreased glucagon-like peptide 1 fasting levels in type 2 diabetes. *Diabetes Care.* **26**(1):252.

Li, C., Li, X., Han, H., Cui, H., Peng, M., Wang, G. and Wang, Z. (2016). Effect of probiotics on metabolic profiles in type 2 diabetes mellitus: A

meta-analysis of randomized, controlled trials. *Medicine (Baltimore)*. **95**(26):e4088.

Li, Y., Hansotia, T., Yusta, B., Ris, F., Halban, P. A. and Drucker, D. J. (2003). Glucagon-like peptide-1 receptor signaling modulates beta cell apoptosis. *J. Biol. Chem.* **278**(1):471–478.

Liddle, R. A., Rushakoff, R. J., Morita, E. T., Beccaria, L., Carter, J. D. and Goldfine, I. D. (1988). Physiological role for cholecystokinin in reducing postprandial hyperglycemia in humans. *J. Clin. Invest.* **81**(6):1675–1681.

Lieverse, R. J., Jansen, J. B., Masclee, A. M. and Lamers, C. B. (1995). Effects of somatostatin on human satiety. *Neuroendocrinology.* **61**(2):112–116.

Ling, Z., Wu, D., Zambre, Y., Flamez, D., Drucker, D. J., Pipeleers, D. G. and Schuit, F. C. (2001). Glucagon-like peptide 1 receptor signaling influences topography of islet cells in mice. *Virchows Archiv.* **438**(4):382–387.

Little, T. J., Horowitz, M. and Feinle-Bisset, C. (2007). Modulation by high-fat diets of gastrointestinal function and hormones associated with the regulation of energy intake: Implications for the pathophysiology of obesity. *Am. J. Clin. Nutr.* **86**(3):531–541.

Long, R. G., Christofides, N. D., Fitzpatrick, M. L., O'Shaughnessy, D. J. and Bloom, S. R. (1982). Effects of intravenous somatostatin and motilin on the blood glucose and hormonal response to oral glucose. *Eur. J. Clin. Invest.* **12**(4):331–336.

Lopes, L. S., Schwartz, R. P., Ferraz-de-Souza, B., da Silva, M. E., Corrêa, P. H. and Nery, M. (2015). The role of enteric hormone GLP-2 in the response of bone markers to a mixed meal in postmenopausal women with type 2 diabetes mellitus. *Diabetol Metab. Syndr.* **7**:13.

Lund, A., Vilsbøll, T., Bagger, J. I., Holst, J. J. and Knop, F. K. (2011). The separate and combined impact of the intestinal hormones, GIP, GLP-1, and GLP-2, on glucagon secretion in type 2 diabetes. *Am. J. Physiol. Endocrinol Metab.* **300**(6):E1038–E1046.

Ma, H. T., Kato, M. and Tatemoto, K. (1996). Effects of pancreastatin and somatostatin on secretagogues-induced rise in intracellular free calcium in single rat pancreatic islet cells. *Regulatory Peptides.* **61**(2):143–148.

Marco, J., Correas, I., Zulueta, M. A., Vincent, E., Coy, D. H., Comaru-Schally, A. M. and Schally, A. V., Rodríguez-Arnao, M. D., Gómez-Pan, A. (1983). Inhibitory effect of somatostatin-28 on pancreatic polypeptide, glucagon and insulin secretion in normal man. *Horm Metab Res.* **15**(8):363–366.

Markianos, M., Evangelopoulos, M. E., Koutsis, G. and Sfagos, C. (2013). Elevated CSF serotonin and dopamine metabolite levels in overweight subjects. *Obesity (Silver Spring).* **21**(6):1139–1142.

Marks, S. J., Moore, N. R., Clark, M. L., Strauss, B. J. and Hockaday, T. D. (1996). Reduction of visceral adipose tissue and improvement of metabolic indices: Effect of dexfenfluramine in NIDDM. *Obes. Res.* **4**(1):1–7.

Matikainen, N., Björnson, E., Söderlund, S., Borén, C., Eliasson, B., Pietiläinen, K. H., Bogl, L. H., Hakkarainen, A., Lundbom, N., Rivellese, A., Riccardi, G., Després, J. P., Alméras, N., Holst, J. J., Deacon, C. F., Borén, J. and Taskinen, M. R. (2016). Minor contribution of endogenous GLP-1 and GLP-2 to postprandial lipemia in obese men. *PLoS One.* **11**(1):e0145890.

Mazidi, M., Rezaie, P., Kengne, A. P., Mobarhan, M. G. and Ferns, G. A. (2016). Gut microbiome and metabolic syndrome. *Diabetes Metab Syndr.* **10**(2–1):S150–S157.

Mefford, I. N., Mefford, J. T. and Burris, C. A. (2012). Improved diabetes control and pancreatic function in a type 2 diabetic after omeprazole administration. *Case Reports in Endocrinology.* **2012**:468609.

Meier, J. J., Gallwitz, B., Schmidt, W. E. and Nauck, M. A.(2002). Glucagon-like peptide 1 as a regulator of food intake and body weight: Therapeutic perspectives. *Eur. J. Pharmacol.* **440**(2–3):269–279.

Meier, J. J., Gallwitz, B., Siepmann, N., Holst, J. J., Deacon, C. F., Schmidt, W. E. and Nauck, M. A. (2003). Gastric inhibitory polypeptide (GIP) dose-dependently stimulates glucagon secretion in healthy human subjects at euglycaemia. *Diabetologia.* **46**(6):798–801.

Meier, J. J., Hücking, K., Holst, J. J., Deacon, C. F., Schmiegel, W. H. and Nauck, M. A. (2001). Reduced insulinotropic effect of gastric inhibitory polypeptide in first-degree relatives of patients with type 2 diabetes. *Diabetes.* **50**(11):2497–2504.

Meier, J. J., Nauck, M. A., Pott, A., Heinze, K., Goetze, O., Bulut, K., Schmidt, W. E., Gallwitz, B. and Holst, J. J. (2006). Glucagon-like peptide 2 stimulates glucagon secretion, enhances lipid absorption, and inhibits gastric acid secretion in humans. *Gastroenterology.* **130**(1):44–54.

Meier, J. J., Gallwitz, B., Kask, B., Deacon, C. F., Holst, J. J., Schmidt, W. E. and Nauck, M. A. (2004). Stimulation of insulin secretion by intravenous bolus injection and continuous infusion of gastric inhibitory polypeptide in patients with type 2 diabetes and healthy control subjects. *Diabetes.* **53**(3):S2204.

Migdalis, L., Thomaides, T., Chairopoulos, C., Kalogeropoulou, C., Charalabides, J. and Mantzara, F. (2001). Changes of gastric emptying rate and gastrin levels are early indicators of autonomic neuropathy in type II diabetic patients. *Clin. Auton. Res.* **11**(4):259–263.

Milewicz, A., Mikulski, E. and Bidzińska, B. (2000). Plasma insulin, cholecystokinin, galanin, neuropeptide Y and leptin levels in obese women with and without type 2 diabetes mellitus. *Int. J. Obes. Relat. Metab. Disord.* **24**(2):S152–S153.

Miyawaki, K., Yamada, Y., Ban, N., Ihara, Y., Tsukiyama, K., Zhou, H. and Seino, Y. (2002). Inhibition of gastric inhibitory polypeptide signaling prevents obesity. *Nature Med.* **8**(7):738–742.

Miyazaki, K., Funakoshi, A. and Ibayashi, H. (1986).Plasma somatostatin-like immunoreactivity responses to a mixed meal and the heterogeneity in healthy and non-insulin-dependent (NIDDM) diabetics. *Endocrinol Jpn.* **33**(1):51–59.

Monteleone, P., Piscitelli, F., Scognamiglio, P., Monteleone, A. M., Canestrelli, B., Di Marzo, V. and Maj, M. (2012). Hedonic eating is associated with increased peripheral levels of ghrelin and the endocannabinoid 2-arachidonoyl-glycerol in healthy humans: A pilot study. *J. Clin. Endocrinol Metab.* **97**(6):E917–E924.

Mul, J. D., Begg, D. P., Barrera, J. G., Li, B., Matter, E. K., D'Alessio, D. A. and Sandoval, D. A. (2013). High-fat diet changes the temporal profile of GLP-1 receptor-mediated hypophagia in rats. *Am. J. Physiol. Regul. Integr. Comparat. Physiol.* **305**(1):R68–R77.

Müller, T. D., Nogueiras, R., Andermann, M. L., Andrews, Z. B., Anker, S. D., Argente, J. and Tschöp, M. H. (2016). Ghrelin. *Molec. Metab.* **4**(6):437–460.

Mumphrey, M. B., Patterson, L. M., Zheng, H. and Berthoud, H. R. (2013). Roux-en-Y gastric bypass surgery increases number but not density of CCK-, GLP-1-, 5-HT-, and neurotensin-expressing enteroendocrine cells in rats. *Neurogastroenterol. Motility Off. J. Eur. Gastrointest. Motil. Soc.* **25**(1):e70–e79.

Nakano, I., Funakoshi, A., Shinozaki, H., Miyazaki, K., Ibayashi, H., Tateish, I. K. and Hamaoka. (1986). Thigh plasma cholecystokinin response following ingestion of test meal by patients with non-insulin dependent diabetes mellitus. *Regul. Pept.* **14**(3):229–236.

Nam, J. S., Nam, J. Y., Yoo, J. S., Cho, M., Park, J. S., Ahn, C. W., … Lee, H. C. (2010). The effect of mosapride (5HT-4 receptor agonist) on insulin sensitivity and GLUT4 translocation. *Diabetes Res. Clin. Pract.* **87**(3):329–334.

Natalicchio, A., De Stefano, F., Orlando, M. R., Melchiorre, M., Leonardini, A., Cignarelli, A. and Giorgino, F. (2010). Exendin-4 prevents c-Jun N-terminal protein kinase activation by tumor necrosis factor-alpha (TNFalpha) and inhibits TNFalpha-induced apoptosis in insulin-secreting cells. *Endocrinology.* **151**(5):2019–2029.

Natalicchio, A., Labarbuta, R., Tortosa, F., Biondi, G., Marrano, N., Peschechera, A. and Giorgino, F. (2013). Exendin-4 protects pancreatic beta cells from palmitate-induced apoptosis by interfering with GPR40 and the MKK4/7 stress kinase signalling pathway. *Diabetologia.* **56**(11):2456–2466.

Nauck, M., Stöckmann, F., Ebert, R. and Creutzfeldt, W. (1986). Reduced incretin effect in type 2 (non-insulin-dependent) diabetes. *Diabetologia.* **29**(1):46–52.

Nauck, M. A, Niedereichholz, U., Ettler, R., Holst, J. J., Orskov, C., Ritzel, R. and Schmiegel, W. H. (1997). Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. *Am. J. Physiol.* **273**(5 Pt 1):E981–E988.

Nauck, M. A., Bartels, E., Orskov, C., Ebert, R. and Creutzfeldt, W. (1993). Additive insulinotropic effects of exogenous synthetic human gastric inhibitory polypeptide and glucagon-like peptide-1-(7–36) amide infused at near-physiological insulinotropic hormone and glucose concentrations. *J. Clin. Endocrinol Metab.* **76**(4):912–917.

Nauck, M.A., Heimesaat, M.M., Orskov, C., Holst, J.J., Ebert, R. and Creutzfeldt, W.(1993). Preserved incretin activity of glucagon-like peptide 1 [7–36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. *J. Clin. Invest.* **91**(1):301–307.

Nauck, M. A., Kleine, N., Orskov, C., Holst, J. J., Willms, B. and Creutzfeldt, W. (1993). Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7–36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia.* **36**(8):741–744.

Neish, A. S. (2009). Microbes in gastrointestinal health and disease. *Gastroenterology.* **136**: 65–80.

Nicholson, J. K., Holmes, E., Kinross, J., Burcelin, R., Gibson, G., Jia, W., et al. (2012). Host-gut microbiota metabolic interactions. *Science.* **336**:1262–1267.

Omar, B., Ahlkvist, L., Yamada, Y., Seino, Y. and Ahrén, B. (2016). Incretin hormone receptors are required for normal beta cell development and function in female mice. *Peptides.* **79**:58–65.

Orskov, C., Holst, J. J. and Nielsen, O. V. (1988). Effect of truncated glucagon-like peptide-1 [proglucagon-(78–107) amide] on endocrine secretion from pig pancreas, antrum, and nonantral stomach. *Endocrinology.* **123**(4):2009–2013.

Pace, C. S. and Tarvin, J. T. (1981). Somatostatin: Mechanism of action in pancreatic islet beta-cells. *Diabetes.* **30**(10):836–42.

Pace, C. S., Murphy, M., Conant, S. and Lacy, P. E. (1977). Somatostatin inhibition of glucose-induced electrical activity in cultured rat islet cells. *Am. J. Physiol.* **233**(5):C165–C171.

Panwar, H., Rashmi, H. M., Batish, V. K., et al. (2013). Probiotics as potential biotherapeutics in the management of type 2 diabetes: Prospects and perspectives. *Diab./Metab. Res. Rev.* **29**(2):103–112.

Pedersen, H. K., Gudmundsdottir, V., Nielsen, H. B., Hyotylainen, T., Nielsen, T., Jensen, B. A., Forslund, K., Hildebrand, F., Prifti, E., Falony, G., Le Chatelier, E., Levenez, F., Doré, J., Mattila, I., Plichta, D. R., Pöhö, P., Hellgren, L.I., Arumugam, M., Sunagawa, S., Vieira-Silva, S., Jørgensen, T, Holm, J. B., Trošt, K., Meta, HIT, Consortium, Kristiansen, K., Brix, S., Raes, J., Wang, J., Hansen, T., Bork, P., Brunak, S., Oresic, M., Ehrlich, S. D., Pedersen, O. (2016). Human gut microbes impact host serum metabolome and insulin sensitivity. *Nature.* **535**(7612):376–381.

Pedersen, J., Ugleholdt, R. K., Jorgensen, S. M., Windeløv, J. A., Grunddal, K. V, Schwartz, T. W., Füchtbauer, E. M., Poulsen, S. S., Holst, P. J. and Holst, J. J. (2013). Glucose metabolism is altered after loss of L cells and α-cells but not influenced by loss of K cells. *Am. J. Physiol. Endocrinol. Metab.* **304**:E60–E73.

Pestell, R. G., Crock, P. A., Ward, G. M., Alford, F. P., Best, J. D. (1989). Fenfluramine increases insulin action in patients with NIDDM. *Diab. Care.* **12**(4):252–258.

Portela-Gomes, G. M., Grimelius, L., Westermark, P. and Stridsberg, M. (2010). Somatostatin receptor subtypes in human type 2 diabetic islets. *Pancreas.* **39**(6):836–842.

Pöykkö, S. M., Kellokoski, E., Hörkkö, S., Kauma, H., Kesäniemi, Y. A. and Ukkola, O. (2003). Low plasma ghrelin is associated with insulin resistance, hypertension, and the prevalence of type 2 diabetes. *Diabetes.* **52**(10):2546–2553.

Price, J. C., Kelley, D. E., Ryan, C. M., Meltzer, C. C., Drevets, W. C., Mathis, C. A., Mazumdar, S. and Reynolds, C. F. (2002). Evidence of increased serotonin-1A receptor binding in type 2 diabetes: A positron emission tomography study. *Brain Res.* **927**(1):97–103.

Proietto, J., Thorburn, A. W., Fabris, S. and Harrison, L. C. (1994). Effects of dexfenfluramine on glucose turnover in non-insulin-dependent diabetes mellitus. *Diabetes Res. Clin. Pract.* **23**(2):127–134.

Psichas, A., Sleeth, M. L., Murphy, K. G., Brooks, L., Bewick, G. A., Hanyaloglu, A. C. and Frost, G. (2015). The short chain fatty acid propionate stimulates GLP-1 and PYY secretion via free fatty acid receptor 2 in rodents. *Int. J. Obesity.* **39**(3):424–429.

Qin, J., Li, Y., Cai, Z., et al. (2012).A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature.* **490**:55–60.

Rachman, J., Barrow, B. A., Levy, J. C. and Turner, R. C. (1997). Near-normalisation of diurnal glucose concentrations by continuous administration of glucagon-like peptide-1 (GLP-1) in subjects with NIDDM. *Diabetologia.* **40**(2):205–211.

Rachman, J., Gribble, F. M., Barrow, B. A., Levy, J. C., Buchanan, K. D. and Turner, R. C.(1996). Normalization of insulin responses to glucose by overnight infusion of glucagon-like peptide 1 (7–36) amide in patients with NIDDM. *Diabetes.* **45**(11):1524–1530.

Rehfeld, J. F. (1971). Effect of gastrin and its C-terminal tetrapeptide on insulin secretion in man. *Acta Endocrinol (Copenh).* **66**(1):169–176.

Rehfeld, J. F. and Stadil, F. (1973). The effect of gastrin on basal- and glucose-stimulated insulin secretion in man. *J. Clin. Invest.* **52**(6):1415–1426.

Rooman, I. and Bouwens, L. (2004). Combined gastrin and epidermal growth factor treatment induces islet regeneration and restores normoglycaemia in C57Bl6/J mice treated with alloxan. *Diabetologia.* **47**(2):259–265.

Rubino, F., R'bibo, S. L., del Genio, F., Mazumdar, M. and McGraw, T. E. (2012). Metabolic surgery: The role of the gastrointestinal tract in diabetes mellitus. *Nat. Rev. Endocrinol.* **6**(2):102–109.

Rubino, F., Zizzari, P., Tomasetto, C., Bluet-Pajot, M. T., Forgione, A., Vix, M. and Marescaux, J. (2005). The role of the small bowel in the regulation of circulating ghrelin levels and food intake in the obese Zucker rat. *Endocrinology.* **146**(4):1745–1751.

Rushakoff, R. A., Goldfine, I. D., Beccaria, L. J., Mathur, A., Brand, R. J. and Liddle, R. A. (1993). Reduced postprandial cholecystokinin (CCK) secretion in patients with noninsulin-dependent diabetes mellitus: Evidence for a role for CCK in regulating postprandial hyperglycemia. *J. Clin. Endocrinol. Metab.* **76**(2):489–493.

Rushakoff, R. J, Goldfine, I. D., Carter, J. D. and Liddle, R. A. (1987). Physiological concentrations of cholecystokinin stimulate amino acid-induced insulin release in humans. *J. Clin. Endocrinol. Metab.* **65**(3):395–401.

Sarson, D. L., Wood, S. M., Kansal, P. C. and Bloom, S. R. (1984). Glucose-dependent insulinotropic polypeptide augmentation of insulin. Physiology or pharmacology?. *Diabetes.* **33**(4):389–393.

Sasaki, S., Miyatsuka, T., Matsuoka, T., Takahara, M., Yamamoto, Y., Yasuda, T. and Shimomura, I. (2015). Activation of GLP-1 and gastrin signalling induces in vivo reprogramming of pancreatic exocrine cells into beta cells in mice. *Diabetologia.* **58**(11):2582–2591.

Scheen, A. J., Paolisso, G., Salvatore, T., Lefèbvre, P. J. (1991). Improvement of insulin-induced glucose disposal in obese patients with NIDDM after 1-wk treatment with d-fenfluramine. *Diabetes Care.* **14**(4):325–332.

Schirra, J., Houck, P., Wank, U., Arnold, R., Göke, B. and Katschinski, M. (2000). Effects of glucagon-like peptide-1(7–36)amide on antro-pyloro-duodenal motility in the interdigestive state and with duodenal lipid perfusion in humans. *Gut.* **46**(5):622–631.

Schmidt, W. E., Siegel, E. G. and Creutzfeldt, W. (1985). Glucagon-like peptide-1 but not glucagon-like peptide-2 stimulates insulin release from isolated rat pancreatic islets. *Diabetologia.* **28**(9): 704–707.

Scrocchi, L. A., Hill, M. E., Saleh, J., Perkins, B. and Drucker, D. J. (2000). Elimination of glucagon-like peptide 1R signaling does not modify weight gain and islet adaptation in mice with combined disruption of leptin and GLP-1 action. *Diabetes.* **49**(9):1552–1560.

Sekhar, M. S. and Unnikrishnan, M. K. (2015). Probiotic research for diabetes prevention. *Nutrition.* **31**(1):248.

Shi, X., Zhou, F., Li, X., Chang, B., Li, D., Wang, Y. and Guan, X. (2013). Central GLP-2 enhances hepatic insulin sensitivity via activating PI3K signaling in POMC neurons. *Cell Metab.* **18**(1):86–98.

Shi, Y.-C., Loh, K., Bensellam, M., Lee, K., Zhai, L., Lau, J. and Herzog, H. (2015). Pancreatic PYY is critical in the control of insulin secretion and glucose homeostasis in female mice. *Endocrinology.* **156**(9):3122–3136.

Shimizu, H., Eldar, S., Heneghan, H. M., Schauer, P. R., Kirwan, J. P. and Brethauer, S. A. (2014). The effect of selective gut stimulation on glucose metabolism after gastric bypass in the Zucker diabetic fatty rat model. Surgery for obesity and related diseases. *Off. J. Am. Soc. Bariatr. Surg.* **10**(1):29–35.

Singh, P. K., Hota, D., Dutta, P., Sachdeva, N., Chakrabarti, A., Srinivasan, A., Singh, I. and Bhansali, A. (2012). Pantoprazole improves glycemic control in type 2 diabetes: A randomized, double-blind, placebo-controlled trial. *J. Clin. Endocrinol. Metab.* **97**(11):E2105–E2108.

Skrha, J., Hilgertová, J., Jarolímková, M., Kunešová, M. and Hill, M. (2010). Meal test for glucose-dependent insulinotropic peptide (GIP) in obese and type 2 diabetic patients. *Physiol. Res.* **59**(5):749–755.

Song, I., Patel, O., Himpe, E., Muller, C. J. F. and Bouwens, L. (2015). Beta cell mass restoration in alloxan-diabetic mice treated with EGF and gastrin. *PloS One.* **10**(10):e0140148.

Sorensen, L. B., Flint, A., Raben, A., Hartmann, B., Holst, J. J. and Astrup, A. (2003). No effect of physiological concentrations of glucagon-like peptide-2 on appetite and energy intake in normal weight subjects. *J. Int. Assoc. Study Obesity.* **27**(4):450–456.

Starosel'tseva, L. K., Kniazeva, A. P., Belovalova, I. M. and Abduraimova, G. R. (1988).The role of gastrin in regulating insulin and glucagon secretion in patients with diabetes mellitus. *Probl. Endokrinol (Mosk).* **34**(4):20–25.

Steiner, C., Othman, A., Saely, C. H., Rein, P., Drexel, H., von Eckardstein, A., Rentsch, K. M. (2011). Bile acid metabolites in serum: Intraindividual variation and associations with coronary heart disease, metabolic syndrome and diabetes mellitus. *PloS One.* **6**:e25006.

Steinert, R. E., Poller, B., Castelli, M. C., Drewe, J. and Beglinger, C. (2010). Oral administration of glucagon-like peptide 1 or peptide YY 3–36 affects food intake in healthy male subjects. *Am. J. Clin. Nutr.* **6**(11):e25006.

Stenman, L. K., Waget, A., Garret, C., Klopp, P., Burcelin, R., Lahtinen, S. (2014). Potential probiotic *Bifidobacterium animalis* ssp. lactis 420 prevents weight gain and glucose intolerance in diet-induced obese mice. *Benef Microbes.* **5**(4):437–445.

Stewart, G. O., Stein, G. R., Davis, T. M. and Findlater, P. (1993). Dexfenfluramine in type II diabetes: Effect on weight and diabetes control. *Med. J. Aust.* **158**(3):167–169.

Strowski, M. Z., Parmar, R. M., Blake, A. D. and Schaeffer, J. M. (2000). Somatostatin inhibits insulin and glucagon secretion via two receptors subtypes: An in vitro study of pancreatic islets from somatostatin receptor 2 knockout mice. *Endocrinology.* **141**(1):111–117.

Suarez-Pinzon, W. L., Power, R. F., Yan, Y., Wasserfall, C., Atkinson, M. and Rabinovitch, A. (2008). Combination therapy with glucagon-like peptide-1 and gastrin restores normoglycemia in diabetic NOD mice. *Diabetes.* **57**(12):3281–3288.

Sun, Y., Asnicar, M., Saha, P. K., Chan, L. and Smith, R. G. (2006). Ablation of ghrelin improves the diabetic but not obese phenotype of ob/ob mice. *Cell Metab.* **3**(5):379–386.

Tamborlane, W. V., Sherwin, R. S., Hendler, R. and Felig, P. (1977). Metabolic effects of somatostatin in maturity-onset diabetes. *N. Engl. J. Med.* **297**(4):181–183.

Tatarkiewicz, K., Hargrove, D. M., Jodka, C. M., Gedulin, B. R., Smith, P. A., Hoyt, J. A., and Parkes, D. G. (2014). A novel long-acting glucose-dependent insulinotropic peptide analogue: Enhanced efficacy in normal and diabetic rodents. *Diab. Obes. Metab.* **16**(1):75–85.

Tellez, N. and Montanya, E. (2014). Gastrin induces ductal cell dedifferentiation and beta-cell neogenesis after 90% pancreatectomy. *J. Endocrinol.* **223**(1):67–78.

Tellez, N., Joanny, G., Escoriza, J., Vilaseca, M. and Montanya, E. (2011). Gastrin treatment stimulates beta-cell regeneration and improves glucose tolerance in 95% pancreatectomized rats. *Endocrinology.* **152**(7):2580–2588.

Terry, N. A., Walp, E. R., Lee, R. A., Kaestner, K. H. and May, C. L. (2014). Impaired enteroendocrine development in intestinal-specific Islet1 mouse mutants causes impaired glucose homeostasis. *Am. J. Physiol. Gastrointest. Liver Physiol.* **307**(10):G979–G991.

Toft-Nielsen, M. B., Damholt, M. B., Madsbad, S., Hilsted, L. M., Hughes, T. E., Michelsen, B. K. and Holst, J. J. (2001). Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. *J. Clin. Endocrinol. Metab.* **86**(8):3717–3723.

Tong, J., Prigeon, R. L., Davis, H. W., Bidlingmaier, M., Kahn, S. E., Cummings, D. E. and D'Alessio, D. (2010). Ghrelin suppresses glucose-stimulated insulin secretion and deteriorates glucose tolerance in healthy humans. *Diabetes.* **59**(9):2145–2151.

Trimble, E. R., Gerber, P. P. and Renold, A. E. (1981). Abnormalities of pancreatic somatostatin secretion corrected by in vivo insulin treatment of streptozotocin-diabetic rats. *Diabetes.* **30**(10):865–867.

Turnbaugh, P. J, Ridaura, V. K., Faith, J. J., Rey, F. E., Knight, R. and Gordon, J. I. (2009). The effect of diet on the human gut microbiome: A metagenomic analysis in humanized gnotobiotic mice. *Sci. Transl. Med.* **1**(6):6–14.

Turnbaugh, P. J., B̆ackhed, F., Fulton, L. and Gordon, J. I. (2008). Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host. Microbe.* **3**:213–223.

Ueno, H., Shiiya, T., Mizuta, M., Mondal, S. M. and Nakazato, M. (2007). Plasma ghrelin concentrations in different clinical stages of diabetic complications and glycemic control in Japanese diabetics. *Endocr. J.* **54**(6):895–902.

Ueno, N., Inui, A., Asakawa, A., Takao, F., Komatsu, Y., Kotani, K. and Kasuga, M. (2002). Mosapride, a 5HT-4 receptor agonist, improves insulin sensitivity and glycaemic control in patients with Type II diabetes mellitus. *Diabetologia.* **45**(6):792–797.

Ukkola, O. H., Puurunen, V. P., Piira, O. P., Niva, J. T., Lepojärvi, E. S., Tulppo, M. P. and Huikuri, H. V. (2011). High serum fasting peptide YY (3–36) is associated with obesity-associated insulin resistance and type 2 diabetes. *Regul. Pept.* **170**(1–3):38–42.

Urbano, F., Filippello, A., Di Pino, A., Barbagallo, D., Di Mauro, S., Pappalardo, A. and Piro, S. (2016). Altered expression of uncoupling protein 2 in GLP-1-producing cells after chronic high glucose exposure: Implications for the pathogenesis of diabetes mellitus. *Am. J. Physiol. Cell Physiol.* **310**(7):C558–C567.

Utzschneider, K. M., Kratz, M., Damman, C. J. and Hullarg, M. (2016). Mechanisms linking the gut microbiome and glucose metabolism. *J. Clin. Endocrinol. Metab.* **101**(4):1445–1454.

Vamvini, M. T., Hamnvik, O.-P., Sahin-Efe, A., Gavrieli, A., Dincer, F., Farr, O. M. and Mantzoros, C. S. (2016). Differential effects of oral and intravenous lipid administration on key molecules related to energy homeostasis. *J. Clin. Endocrinol. Metab.* **101**(5):1989–1997.

Vella, A. (2013). Enteroendocrine secretion after Roux-en-Y gastric bypass: Is it important? Neurogastroenterology and motility. *Off. J. Eur. Gastrointestinal Motil. Soc.* **25**(1):1–3.

Vilsboll, T., Krarup, T., Deacon, C. F., Madsbad, S. and Holst, J. J. (2001). Reduced postprandial concentrations of intact biologically active glucagon-like peptide 1 in type 2 diabetic patients. *Diabetes.* **50**(3):609–613.

Vilsboll, T., Krarup, T., Madsbad, S. and Holst, J.J. (2002). Defective amplification of the late phase insulin response to glucose by GIP in obese type II diabetic patients. *Diabetologia.* **45**:1111–1119.

Vincent, R. P., Omar, S., Ghozlan, S., Taylor, D. R., Cross, G., Sherwood, R. A., Fandriks, L., Olbers, T., Werling, M., Alaghband-Zadeh, J., le Roux, C. W.(2013). Higher circulating bile acid concentrations in obese patients with type 2 diabetes. *Ann. Clin. Biochem.* **50**(Pt 4):360–364.

Vrieze, A., Van Nood, E., Holleman, F., Salojarvi, J., Kootte, R. S., Bartelsman, J. F., et al. (2012). Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology.* **143**(4):913–916.e7.

Ward, F. R., Leblanc, H. and Yen, S. S. (1977). The inhibitory effect of somatostatin on growth hormone, insulin and glucagon secretion in diabetes mellitus. *J. Clin. Endocrinol Metab.* **41**(3):527–532.

Weintraub, M., Sundaresan, P. R., Madan, M., Schuster, B., Balder, A., Lasagna, L. and Cox, C. (1992). Long-term weight control study. I (weeks 0 to 34). The enhancement of behavior modification, caloric restriction, and exercise by fenfluramine plus phentermine versus placebo. *Clin. Pharmacol. Ther.* **51**(5):586–594.

Weltzin, T. E., Fernstrom, M. H., Fernstrom, J. D., Neuberger, S. K. and Kaye, W. H. (1995). Acute tryptophan depletion and increased food intake and irritability in bulimia nervosa. *Am. J. Psychiatry.* **152**(11):1668–1671.

Wettgren, A., Schjoldager, B., Mortensen, P. E., Myhre, J., Christiansen, J. and Holst, J. J.(1993). Truncated GLP-1 (proglucagon 78-107-amide) inhibits gastric and pancreatic functions in man. *Dig. Dis. Sci.* **38**(4):665–673.

Widenmaier, S. B., Kim, S.-J., Yang, G. K., De Los Reyes, T., Nian, C., Asadi, A. and McIntosh, C. H. S. (2010). A GIP receptor agonist exhibits β-cell anti-apoptotic actions in rat models of diabetes resulting in improved β-cell function and glycemic control. *Plos One.* **5**(3):e9590.

Williams, D. L., Hyvarinen, N., Lilly, N., Kay, K., Dossat, A., Parise, E. and Torregrossa, A.M. (2011). Maintenance on a high-fat diet impairs the anorexic response to glucagon-like-peptide-1 receptor activation. *Physiology Behavior.* **103**(5):557–564.

Willms, B., Werner, J., Holst, J. J., Orskov, C., Creutzfeldt, W. and Nauck, M. A. (1996). Gastric emptying, glucose responses, and insulin

secretion after a liquid test meal: Effects of exogenous glucagon-like peptide-1 (GLP-1)-(7–36) amide in type 2 (noninsulin-dependent) diabetic patients. *J. Clin. Endocrinol. Metab.* **81**(1):327–332.

Wozniak, K. M. 1., Linnoila, M. (1991). Hyperglycemic properties of serotonin receptor antagonists. *Life Sci.* **49**(2):101–109.

Wren, A. M., Seal, L. J., Cohen, M. A., Brynes, A. E., Frost, G. S., Murphy, K. G., Dhillo, W. S., Ghatei, M. A. and Bloom, S. R. (2001). Ghrelin enhances appetite and increases food intake in humans. *J. Clin. Endocrinol Metab.* **86**(12):5992.

Wright, M., Woodrow, G., O'Brien, S., Armstrong, E., King, N., Dye, L., Blundell, J., Brownjohn, A. and Turney, J. (2004). Cholecystokinin and leptin: Their influence upon the eating behaviour and nutrient intake of dialysis patients. *Nephrol. Dial. Transplant.* **19**(1):133–140.

Yabe, D. and Seino, Y. (2011). Two incretin hormones GLP-1 and GIP: Comparison of their actions in insulin secretion and β cell preservation. *Progress Biophys. Mol. Biol.* **107**(2):248–256.

Yakovlieva, M., Tacheva, T., Mihaylova, S., Tropcheva, R., Trifonova, K., Toleκova, A., Danova, S. and Vlaykova, T. (2015). Influence of *Lactobacillus brevis* 15 and *Lactobacillus plantarum* 13 on blood glucose and body weight in rats after high-fructose diet. *Benef. Microbes.* **6**(4):505–512.

Zhang, S., Wang, S., Hyrc, K. and Wice, B. M. (2013). Metabolic profiling identifies beta-hydroxypyruvate (HP) as a potential mediator of type 2 diabetes mellitus (T2DM) in mice. *Diabetes.* **62**: A524.

Zhang, S., Wang, S., Puhl, M. D., Jiang, X., Hyrc, K. L., Laciny, E., Wallendorf, M. J., Pappan, K. L., Coyle, J. T. and Wice, B. M. (2015). Global biochemical profiling identifies β-hydroxypyruvate as a potential mediator of type 2 diabetes in mice and humans. *Diabetes.* **64**:1383–1394.

Zhang, Y., Ying, B., Shi, L., Fan, H., Yang, D., Xu, D. and Wen, F. (2007). Ghrelin inhibit cell apoptosis in pancreatic beta cell line HIT-T15 via mitogen-activated protein kinase/phosphoinositide 3-kinase pathways. *Toxicology.* **237**(1–3):194–202.