# Physiology of incretins (GIP and GLP-1) and abnormalities in type 2 diabetes

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**Abstract**

Incretin hormones are defined as intestinal hormones released in response to nutrient ingestion, which potentiate the glucose-induced insulin response. In humans, the incretin effect is mainly caused by two peptide hormones, glucose-dependent insulin releasing polypeptide (GIP), and glucagon-like peptide-1 (GLP-1). GIP is secreted by K cells from the upper small intestine while GLP-1 is mainly produced in the enteroendocrine L cells located in the distal intestine. Their effect is mediated through their binding with specific receptors, though part of their biological action may also involve neural modulation. GIP and GLP-1 are both rapidly degraded into inactive metabolites by the enzyme dipeptidyl-peptidase-IV (DPP-IV).

In addition to its effects on insulin secretion, GLP-1 exerts other significant actions, including stimulation of insulin biosynthesis, inhibition of glucagon secretion, inhibition of gastric emptying and acid secretion, reduction of food intake, and trophic effects on the pancreas. As the insulinotropic action of GLP-1 is preserved in type 2 diabetic patients, this peptide was likely to be developed as a therapeutic agent for this disease.

**Résumé**

Physiologie des incrétines (GLP1 et GIP) et anomalies des incrétines dans le diabète de type 2

Les incrétines sont des hormones intestinales libérées en réponse à une prise alimentaire, qui potentialisent la réponse insulinique induite par le glucose. Chez l'homme, l'effet incrétine est essentiellement lié à deux hormones peptidiques, le glucose-dependent insulin releasing polypeptide (GIP) et le glucagon-like peptide-1 (GLP-1). Le GIP est sécrété par les cellules K du duodénum, alors que le GLP-1 est essentiellement sécrété par les cellules intestinales endocrines L situées dans la partie distale de l'intestin. Leur effet est médié *via* leur liaison à des récepteurs spécifiques, mais une partie de leur action biologique pourrait également impliquer des mécanismes régulateurs centraux. Le GIP et le GLP-1 sont tous deux rapidement dégradés en métabolites inactifs par une enzyme, la dipeptidyl-peptidase-IV (DPP-IV).

En sus de ses effets sur la sécrétion d'insuline, le GLP-1 exerce d'autres actions importantes, entre autres, la stimulation de la biosynthèse de l'insuline, l'inhibition de la sécrétion de glucagon, l'inhibition de la vidange gastrique et de la sécrétion acide, la réduction de la prise alimentaire, ainsi que des effets trophiques sur le pancréas. Dans la mesure où l'action insulinotrope du GLP-1 est conservée chez les patients ayant un diabète de type 2, ce peptide représente une nouvelle approche thérapeutique dans le diabète de type 2.

*Keywords:* Incretin hormones; Glucagon-like peptide-1; Insulin; Type 2 diabetes.

*Mots clés :* Hormones incrétines ; Glucagon-like peptide-1 ; Insuline ; Diabète de type 2.

## 1. Introduction

The concept that factors secreted from the gut participate to the regulation of endocrine secretion was raised as early as the beginning of the 20th century [1]. The term "secretin" was first used to define factors regulating pancreas secretion. Later, the term "incretin" was introduced in the 1920's to describe these potential mediators. The connection

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between the gastrointestinal tract and the endocrine pancreas was confirmed in the 1960s, when insulin became measurable in plasma. Clinical studies showed that for an oral and an intravenous load of glucose producing identical increases in plasma glucose levels, the insulin secretory response was greater when glucose was administered orally. These findings suggested that not only glucose interacted with beta cells in the islets of Langerhans, but also gut factors were released, that stimulated insulin secretion [2].

The incretin effect was finally defined as the phenomenon of oral glucose eliciting a greater insulin response than intravenous glucose infusions, irrespective of the same amount of glucose is infused or an equivalent rise in glycaemia is produced by the parenteral route [3]. The incretin effect account for approximately 50 to 70% of the total insulin secreted after glucose ingestion. In humans, two peptide hormones have been identified as being responsible for the incretin effect, namely glucose-dependent insulin releasing polypeptide, GIP (formerly called gastric inhibitory polypeptide) and glucagon-like peptide-1, GLP-1. GIP and GLP-1 are both secreted in response to food ingestion and both potentiate the glucose-induced insulin response.

GLP-1 previously demonstrated a promising potential in the treatment of diabetes mellitus, showing near normalized glucose levels following intravenous infusions in patients with type 2 diabetes [4-6]. It is now recognized that the biological effects of GLP-1 comprise not only an effect on insulin-secreting cells but also on other pancreatic cells, as well as effects on several extrapancreatic sites. Additionally, trophic effects on the pancreatic islets have been recently discovered in animal models, which make GLP-1 and GLP-1 analogues exciting candidates for diabetes therapy [7].

The aim of the present article is to review the current knowledge on the physiology of the two incretin peptides GIP and GLP-1 and their abnormalities in type 2 diabetes.

## 2. Incretin synthesis, pharmacokinetic and effectors

GIP and GLP-1 are both members of the glucagon peptide superfamily, sharing a close amino acid homology.

GIP is a single 42 amino acid peptide derived form the processing of a 153 amino acid precursor, whose 10 kilobase-spanning gene is located on chromosome 17 in humans [review in [8]] (Fig. 1). GIP is secreted in a single bioactive form by K cells and released from the upper small intestine (duodenum and proximal jejunum), in response to the oral ingestion of carbohydrates and lipids.

GLP-1 is a product of the proglucagon gene, spanning 10 kilobases and located on the long arm of chromosome 2, that encodes not only GLP-1 but also glucagon, GLP-2 and other proglucagon-derived peptides [8] (Fig. 1). Glucagon is the main product of post transcriptional processing of proglucagon in the endocrine pancreas. GLP-1 is produced together with GLP-2 and glicentin (enteroglucagon) as the main pro-

ducts in the enteroendocrine L cells. Despite close structural homology, GLP-2 does not share the same biological action as GLP-1, but rather acts as a regulator of growth in the intestinal tract [review in [9]].

GLP-1 is mainly expressed in mucosal L cells located predominantly in the distal intestine (ileum and colon), and is also expressed in pancreatic alpha cells, as well as in neurons from several brain areas (hypothalamus, pituitary, nucleus of the tractus solitarius, reticular nucleus). GLP-1 is secreted from L cells in two bioactive forms, GLP-1[7-37] and the predominant circulating active form GLP-1[7-36] amide, also called "truncated" GLP-1. Both peptides are equipotent, with a same plasma half-life and identical activity through the same receptor.

Despite the distal location of L-cells in the gastrointestinal tract, GLP-1 is released into the circulation within minutes following oral ingestion of nutrients, suggesting that this prompt release is more indirectly controlled by neural and endocrine factors initiated by nutrient entry in the proximal gastrointestinal tract, rather than directly stimulated by contact of L-cells with nutrients. Although these factors remain largely unknown in humans, experimental studies in rodents suggest that the vagal nerve, through muscarinic receptors M3, is a contributing factor [see review [9]]. However, L cells do exist in the proximal intestine. Recently, the sweet taste receptor subunit T1R3 and the taste G protein gustducin of the tongue, have been shown to be also expressed in enteroendocrine cells and to modulate glucose transport in the enterocytes (*via* the sodium– dependent glucose transporter SGLT1) [10]. Animal models lacking gustducin display defective GLP-1 secretion in response to glucose [11]. *In vitro*, GLP-1 release from a human L cell line, is promoted by sugars and the noncaloric sweetener sucralose, and blocked by the sweet receptor antagonist lactisole or siRNA for alpha-gustducin. Therefore, taste receptors participate in the GLP-1 release in response to glucose [11].

Circulating levels of GIP and GLP-1 are very low in the fasting state, and rapidly increase following food ingestion. Noteworthy recent findings in rats suggest that the intestinal lymph is the preferred medium of release of GLP-1, as the hormone levels in the lymph following nutrient administration were five to six times as higher as that in the portal plasma [12]. This raises the possibility that GLP-1 exerts specific effects mediated in this compartment.

Both GIP and GLP-1 are extensively and rapidly degraded by the enzyme dipeptidyl-peptidase IV (DPP-IV), that cleaves the biologically active forms at the position 2 alanine (N-terminal), resulting in inactive or weak antagonist peptide fragments. The enzyme DPP-IV is widely expressed and can be found in multiple tissues and cell types such as central nervous system, kidney, lung, adrenal gland, liver, intestine, spleen, testis, and pancreas, as well as on the surface of lymphocytes and macrophages. DPP-4 also is found on the surface of endothelial cells, including those lining blood vessels that drain the intestinal mucosa, which are positioned directly adjacent to the sites of GLP-1 secretion

[13]. These findings suggest that the majority of GIP and GLP-1 released in the portal circulation is inactivated by DPP-4 before entry into the systemic circulation. In addition to cell-surface membrane-bound form, DPP-4 also exists as a soluble protein in the circulation. Thus, a minor amount of secreted incretins reach the pancreatic β-cells. When incretins are administered intravenously in normal subjects and in diabetic patients, the plasma half-life ($t_{1/2}$) of exogenous GIP is about 5-7 minutes, while that of intact GLP-1 is only about 1-2 minutes [13,14].

The effects of GIP and GLP-1 are mediated after binding to specific plama membrane receptors. Both GIP and GLP-1 receptors have been cloned. They belong to the 7 trans-membrane-domain receptor family coupled to G-proteins. Binding of GIP and GLP-1 peptides to their respective receptor causes the activation of adenyl cyclase *via* the G protein, and leads to an increase of intracellular cyclic AMP levels. Subsequent activation of protein kinase-A results in a cascade of intracellular events such as increased concentrations of cytosolic $Ca^{2+}$ and, in the case of pancreatic β-cells, enhanced exocytose of insulin-containing granules. Other signalling pathways may also be activated such as MAP kinase, phospho-inositol-phosphate PIP3, and protein kinase B (PKB) pathways [review in [9]].
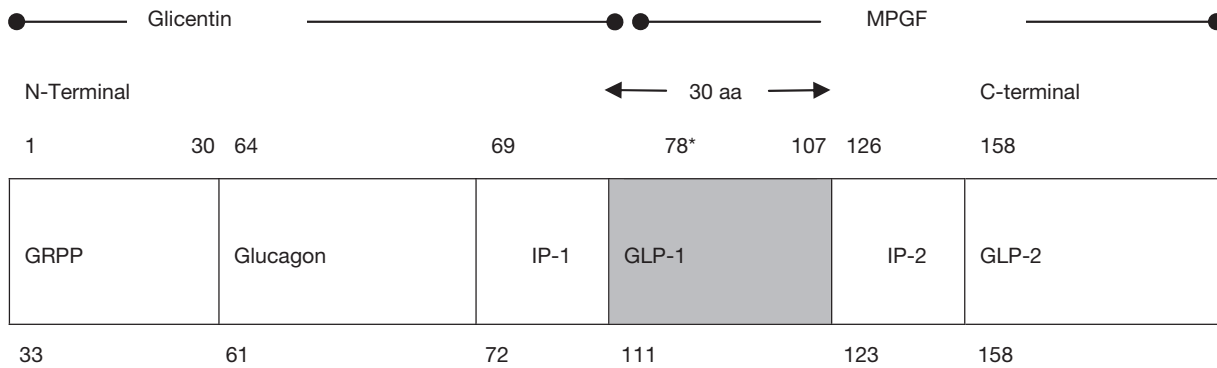
GIP receptors are expressed in the pancreatic islets, gut, adipose tissue, heart, pituitary, adrenal cortex and in several
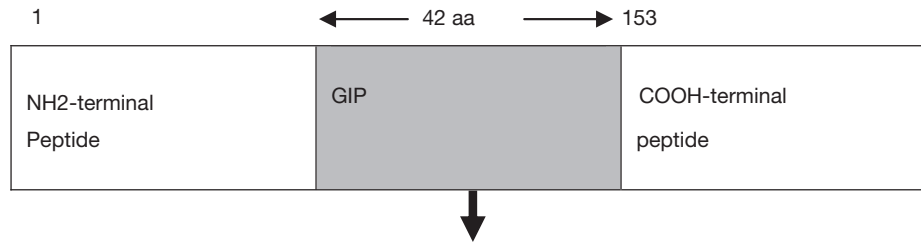


**Fig. 1. Structure of proGIP and Proglucagon, encoding GIP and GLP-1.**

MGPF: major proglucagon-derived fragment; GRPP: glicentin related polypeptide; IP: intervening factor; GLP: Gucagon-like peptide. * indicates the position where GLP-1 is cleaved by the enzyme DPP-IV.

In pancreatic alpha cells, proglucagon is cleaved to produce glucagon and MPGF. Glucagon is contained within the sequence of the 69 amino acid glicentin (enteroglucagon).

In entero-endocrine L cells of the small and large bowel, proglucagon is cleaved into glicentin and two glucagon-like peptides, GLP-1 and GLP-2, separated by an intervening peptide IP-2.

regions of the brain [8]. GLP-1 receptors are expressed in the gastrointestinal tract, endocrine pancreas (alpha and beta cells), lung, kidneys, heart and in several brain areas (hypothalamus, nucleus of the solitary tract, area postrema) [review in [9]].

As described above, most GLP-1 secreted from the gut is already inactivated by DPP-IV upon entry into the capillaries, suggesting that GLP-1 may exert part of its action before it enters the capillaries. Independently of this action, it is likely that the activity of endogenous GLP-1 is also exerted through interaction with sensory afferent nerve fibres relaying in the brain and modulating efferent vagal fibers that, in turn, regulate a number of its biological actions (gastrointestinal secretion and motility, pancreatic secretion).

## 3. Physiological actions of incretins

### 3.1. Physiological actions of GIP (Table 1)

#### 3.1.1. Effects on insulin secretion

GIP exerts glucose-dependent stimulatory effects on insulin secretion in animals and humans [15, 16]. The incretin function of GIP was first studied in dogs and rodents, using GIP antagonists and GIP receptor antisera ("neutralization studies"). When given alone, these compounds induced a reduction in the insulin response to oral glucose; when given concomitantly with exogenous GIP, they attenuated its insulinotropic effects [review in [17]]. In other experi-

mental studies, it was shown that mice lacking the GIP receptor exhibited glucose intolerance after an oral glucose load [18]. As the glucose intolerance found in this experimental model was not very severe, it was concluded that GIP is not the only incretin hormone and that other insulinotropic agents are secreted, which compensate the lack of GIP receptor activation. Results of studies in humans as well as studies in mice lacking both the GIP and the GLP-1 receptors showed an additive effect of GIP and GLP-1 in the incretin effect [19]. In physiological conditions, it appears that smaller loads of rapidly absorbable nutrients would preferentially activate the upper incretin hormone GIP, whereas ingestion of larger meal containing more complex nutrients would also activate the distal incretin GLP-1.

#### 3.1.2. Effect on adipose tissue metabolism

GIP receptors are present on adipocytes [20] and there is experimental evidence indicating that GIP regulates fat metabolism in adipocytes, including enhanced insulin-stimulated incorporation of fatty acids into triglycerides, stimulation of lipoprotein lipase activity, stimulation of fatty acids synthesis. At present, the exact signalling mechanisms mediating the effects of GIP on fat cells are unknown [21].

#### 3.1.3. Other actions

GIP has been shown to promote β-cell proliferation and cell survival in islet cell line studies [22]. In contrast with GLP-1, GIP does not influence pancreatic α-cell secretion of glucagon in humans, nor does it affect gastric emptying.

### 3.2. Physiological actions of GLP-1 (Table 1)

#### 3.2.1. Effects on insulin secretion

GLP-1 stimulates glucose-induced insulin secretion in isolated islets of Langerhans, in the perfused pancreas and in whole organisms, in animals and humans.

It has been demonstrated in rats, that insulin secretory responses to oral intake of nutrients and to intraduodenal glucose were suppressed when using the GLP-1 receptor antagonist exendin 9-39 [8]. In addition, mice lacking the GLP-1 receptor showed fasting hyperglycaemia and abnormal glucose excursion with significantly reduced insulin secretion after a glucose load [19].

In humans, secretion of GLP-1 throughout the day is strongly correlated with the release of insulin [20]. The effect of GLP-1 on insulin secretion is strictly glucose-dependent and there is no effect of GLP-1 on insulin secretion for glucose concentrations below a certain threshold (approximately 4.5 mmol/l).

The incretin activity of GLP-1 has been recognized from studies performed in healthy subjects, using exogenous GLP-1 [24,25]. However, the contribution of the incretin effect in normal subjects is a matter of debate. A number of experimental data suggest that GLP-1 is responsible for a substantial part of the insulin response to oral glucose [17],

Table 1

Summary of the main characteristics of GIP and GLP-1

|  | GIP | GLP-1 |
|---|---|---|
| **Characteristics** | | |
| Peptide | 42 amino acids | 30 amino acids |
| Released from | K cells - duodenum | L cells - ileum and colon |
| Active form | Single bioactive form | Two bioactive forms: (7-37) and (7-36)amid |
| Inactivated by | DPP-IV | DPP-IV |
| **Physiological actions** | | |
| Insulin secretion | Stimulated | Stimulated |
| Insulin biosynthesis | - | Stimulated |
| Beta cell proliferation | Promoted | Promoted |
| Glucagon secretion | - | Inhibited |
| Food intake | - | Reduced |
| Gastrointestinal motility | - | Participates in the ileal brake |
| Cardiac function | Inhibition | Improvement |
| Bone resorption | | Inhibition |
| **In type 2 diabetes** | | |
| Secretion | Normal | Reduced |
| Response | Impaired | Preserved |

whereas other experiments suggest that the contribution might be rather small in normal conditions [26].

### 3.2.2. Effects on insulin biosynthesis

In addition to its effects on insulin secretion, GLP-1 has been shown to stimulate insulin gene transcription and all steps of insulin biosynthesis in isolated β-cells, thereby providing continual supplies of insulin for secretion [review in [27]]. This may be important for maintaining insulin levels during secretion which tends to deplete them.

### 3.2.3. Inhibitory effects on glucagon secretion

GLP-1 is able to suppress glucagon secretion in pancreatic islets, in perfused pancreas and in whole organisms. The mechanism by which GLP-1 inhibits glucagon secretion remains to be elucidated. The inhibitory effect is probably indirectly mediated *via* insulin release and *via* somatostatin secretion. However, a direct effect of GLP-1 is not completely excluded since GLP-1 receptors are expressed on pancreatic α-cells [27].

The inhibitory effects of GLP-1 on glucagon secretion seem to represent an important mechanism for regulating elevated levels of blood glucose. In patients with type 1 diabetes (i.e. who are deprived of insulin), administration of GLP-1 decreased blood glucose levels while the secretion of glucagon was strongly inhibited, suggesting that GLP-1 suppressed the hepatic production of glucose induced by glucagon [28].

The inhibition of glucagon secretion by GLP-1 is glucose-dependent, meaning that GLP-1 administration is unlikely to impair the glucagon counterregulatory response to hypoglycaemia [29].

### 3.2.4. Trophic and protective effects on pancreatic ß-cells

GLP-1 has been shown to exert trophic effects on pancreatic β-cell mass. It stimulates β-cell proliferation and β-cell neogenesis from rat and human pancreatic duct [30]. When given for prolonged periods to normal rodents or to animals with impaired glucose tolerance or diabetes, GLP-1 and its long acting analogue exendin-4 increased β-cell mass. GLP-1 promoted β-cell replication in mice, and stimulated DNA synthesis in cell lines *in vitro*. GLP-1 also promoted the differentiation of precursor of β-cells in the pancreatic duct epithelium. In addition, GLP-1 exhibited anti-apoptotic effects in β-cells of rodent models (Zucker Diabetic Fatty rats). Recent studies have also reported anti-apoptotic effects of GLP-1 on human isolated β-cell gluco-, lipo- and glucolipotixicity, an effect mediated *via* protein kinase B (PKB) activation [31]. Unlike its insulinotropic effect dependent on Protein Kinase A (PKA) pathways, the trophic and survival effects of GLP-1 are mediated through different signalling pathways involving PKB. Animal model of diabetes is associated with endoplasmic reticulum (ER) stress in β-cell. Endoplasmic reticulum stress, also called "unfolded protein response (UPR)" is a complex cellular pathway which takes place in the endoplasmic reticulum in order to care a high rate of protein secreted in the ER. Endoplasmic reticulum stress

is activated in cells that carry out a strong capacity to secrete proteins such as the pancreatic β-cells. Recently, it has been reported that a GLP-1 receptor agonist reduced biochemical markers of islet ER stress *in vivo* [32]. *In vitro*, the agonist also improved survival of rat β-cells and rodent insulinoma cells following ER stress. Furthermore, ER stress-associated β-cell death was also reduced, in a PKA-dependent manner.

Whether GLP-1 also expresses pancreatic trophic properties *in vivo* in humans'remains to be confirmed; nevertheless, these findings raise considerable interest from a clinical perspective, as GLP-1 and GLP-1 analogues could be potentially useful in preserving functional β-cell mass in patients with type 2 diabetes.

### 3.2.5. Effects on the gastrointestinal tract

GLP-1 exerts inhibitory effects on gastrointestinal secretion and motility, particularly on gastric emptying [26]. Administration of GLP-1 at physiological doses in healthy volunteers results in a dose-dependent slowing of gastric emptying and of glucose absorption, which participate in a subsequent reduction of postprandial plasma glucose concentration [26]. This suggests that GLP-1 participate in the "ileal brake" phenomenon, by which nutrients present in the distal part of the small intestine induce a reduction in upper intestinal motility and secretory activity. The actions of GLP-1 on gastrointestinal motility and secretion probably involve neurally-mediated mechanisms, including vago-vagal pathways.

The physiological role of GLP-1 may be to adjust the absorptive capacity of the gut and to adjust the amount of chyme, by slowing gastrointestinal transit and decreasing secretion of digestive enzymes. Under physiological conditions, it is likely that the gastrointestinal effects of GLP-1, (i.e. reduction of gastric secretion and slowing of gastric emptying) are more important than its insulinotropic action [26]. In pathological conditions such as diabetes, the inhibitory effects of GLP-1 on gastrointestinal motility, particularly gastric emptying, are of special interest because they potentially reduce postprandial glucose excursions.

### 3.2.6. Effects on food intake

GLP-1 has been shown to reduce caloric intake and to enhance satiety, these effects being probably related to central mechanisms.

In experimental studies with rodents, intracerebroventricular administration of GLP-1 significantly reduced food ingestion, whereas concomitant injection of the GLP-1 receptor antagonist exendin-9-39 abolished this effect [33]. Significant reduction of food intake and consequently lower weight gain was also observed after the systemic administration of a GLP-1 analogue in rhesus monkeys, in diabetic db/db mice and in Zucker diabetic fatty rats [review in [34]].

In normal subjects, the intravenous administration of GLP-1 above physiological levels induced increased feelings of satiety as well as a reduction of food intake [35]. Similar effects were observed in obese subjects, as well as in patients with type 2 diabetes [36,37]. In type 2 diabetic

patients treated with a subcutaneous infusion of GLP-1 for up to 6 weeks, the reduction of food intake was sustained and associated with a reduction of body weight [38].

The exact mechanism by which peripheral GLP-1 is able to modulate food intake is not completely elucidated [34]. One possibility is that peripheral GLP-1 acts on vagal afferent fibers, where it may modulate GLP-1 neuronal transmission in central nervous system (CNS). This hypothesis is supported by the localization of GLP-1 containing neurons in the nucleus of the tractus solitarius, which projects into thalamic and hypothalamic regions implicated in the control of food intake. Another possibility is that circulating GLP-1 directly reaches GLP-1 receptors located in blood brain barrier-free areas (such as the area postrema and subfornical organ) that in turn, relay to brain nuclei involved in nutrient homeostasis. It is also likely that inhibition of gastric emptying mediated by GLP-1 increases the sensation of fullness and leads to the termination of meal ingestion, thereby participating in the regulation of food intake. Finally nausea, a side effect often observed after administration of exogenous GLP-1, may also be a contributing factor, though the decrease of food intake was observed even in subjects who did not report nausea.

### 3.2.7. Effects on the bone and the heart

GLP-1 can improve endothelial dysfunction in type 2 diabetic subjects with stable coronary heart disease [39]. Additionally, GLP-1 exerts a direct protective effect on the myocardium against ischemia/reperfusion injury in rat models [40]. Importantly, the GLP-1 metabolite GLP-1 [9-36] amide that has no insulinotropic action, could also mediate myocardial glucose uptake, thus improving left ventricular performance in dogs with dilated cardiomyopathy [41].

GLP-1 may control bone resorption. Mice devoid of GLP-1 receptor have cortical osteopenia, bone fragility, increased osteoclast numbers and markers of bone resorption [42]. These effects are corrected by calcitonin treatment, indicating that GLP-1 bone-protective effects may involve a calcitonin-dependent pathway.

### 3.2.8. Other actions

GLP-1 is a potent stimulator of somatostatin secretion from isolated human islets. This effect is not dependent on glucose concentrations [8].

Other actions noteworthy for the glucose homeostasis have been described. GLP-1 can abolish postprandial increase in plasma triglyceride and suppress fasting and meal-related increase in nonesterified fatty acid in normal and type 2 diabetic subjects [38,43].

Recently, Burcelin's group expanded the knowledge on the role of brain GLP-1 in glucose homeostasis using intracerebroventricular injections of GLP-1 agonist/antagonist [44]. They found that in hyperglycaemic conditions, a portal glucose signal leads to the stimulation of brain GLP-1 receptors, which inhibits muscle glucose utilization while favouring hepatic insulin-stimulated glycogen storage. This may constitute a regulatory mechanism preparing for the fasting state. GLP-1 was also recently shown to reduce blood-brain barrier transport of glucose in human, probably by interacting with the GLUT1 transporter and the GLP-1 receptor in the blood-brain barrier [45]. This may be an important neuroprotective mechanism from high glucose levels in postprandial state.

## 4. Incretin secretion and function in type 2 diabetes

The overall incretin effect has been shown to be severely reduced in patients with type 2 diabetes [46,47]. To understand the mechanism of this impairment, many studies have evaluated the secretion of GLP-1 and GIP or the response to exogenous administration of GLP-1 and GIP in type 2 diabetic patients. In these patients, circulating levels of GIP are normal [46,47] or increased [49] in basal and postprandial conditions. In contrast, plasma levels of GLP-1 are reduced in type 2 diabetic patients or in patients with impaired glucose tolerance, as compared to normal subjects, especially when assays detecting intact GLP-1 are used [48,50]. The mechanism of the impaired secretion of GLP-1 is unknown, but several factors such as the severity of diabetes or the body mass index have been suggested to influence GLP-1 secretion. Furthermore, recent reports have shown that the incretin effect is also reduced in patients with secondary diabetes due to chronic pancreatitis, suggesting that it is a consequence rather than a cause of type 2 diabetes [46].

To evaluate the action of incretin in type 2 diabetes, the response to exogenous infusions has been studied, with significant differential results between GIP and GLP-1. Nauck et al. investigated the effects of intravenous infusions of GLP-1 and GIP compared to placebo in mild type 2 diabetic patients versus healthy controls [51]. The insulinotropic response to GIP administration was 54% lower in diabetic patients compared to normal subjects. The precise cellular mechanisms contributing to impaired GIP function in diabetes remain to be elucidated. In contrast to GIP, the insulinotropic response to GLP-1 was similar to that in controls, and its glucagonostatic activity was also preserved. Another study later on confirmed the preservation of the effects of exogenous GLP-1 on insulin secretion, glucagon suppression and ability to decelerate gastric emptying [52]. The different responsiveness is somewhat surprising since both hormones GIP and GLP-1 are very similar (close structural homology, same family of receptors, same signal transduction mechanisms).

In summary, these findings suggest that in patients with type 2 diabetes: 1) the secretion of GLP-1 is impaired while the secretion of GIP is unaffected; 2) GIP administration has very little insulinotropic activity whereas GLP-1 maintains its ability to stimulate glucose-dependent insulin secretion and to inhibit glucagon secretion as well. Consequently, GLP-1 as well as GLP-1 receptor agonists appeared interesting potential therapeutic agents for type 2 diabetes.

## 5. New developments on the role of incretin dysfunction in the pathogenesis of type 2 diabetes

Despite data suggesting that the decreased incretin effect in type 2 diabetes may be a consequence rather than a cause of the diabetic state [46], the implication of impaired incretion function in the etiology of type 2 diabetes has been very recently a subject of debate. It has been suggested to be the mediator of a genetic factor that confers a high risk for type 2 diabetes. The gene of Transcription factor-7-like 2 (*TCF7L2*) encodes for a transcription factor that binds to β-catenin to induce transcription of a number of genes, including intestinal proglucagon's. Variants of TCF7L2 have been reproducibly shown to be strongly associated with type 2 diabetes and impaired insulin secretion in various populations [53-55]. Given that the incretin GLP-1 stems from proglucagon, many recent reports investigated the putative role of altered incretin effect in impaired insulin secretion in carriers of TCF7L2 variants. The first study showed that the incretin effect was significantly reduced by 20% in carriers of the risk (T) allele with abnormal glucose tolerance or type 2 diabetes, compared to non carriers [56]. Another study investigated the role of GLP-1 [57]. Whereas the GLP-1 concentration *per se* was similar in carriers and non carriers of the risk allele, GLP-1 infusion showed a significant reduction in GLP-1-induced insulin secretion in carriers of risk allele [57]. Interestingly, TCF7L2 has been shown to regulate β-cell survival and function in isolated human pancreatic islets [58].

Impairment of incretin effect may therefore mediate the diabetogenic effect of TCF7L2 polymorphisms. This seems to be through a reduction of GLP-1 action without alteration of GLP-1 secretion. However, understanding the precise mechanisms governing this phenomenon requires further investigations.

## 6. Conclusion

GIP and GLP-1 are both incretin hormones secreted in response to meal ingestion that potentiate the glucose-induced insulin response. In addition, GLP-1 plays an important role in inhibiting glucagon secretion. Trophic effects of GLP-1 on pancreatic beta-cells were also demonstrated in animal models. Other physiological actions of GLP-1 include the inhibition of gastrointestinal secretion and gastric emptying, and the reduction of food intake. In contrast with GIP, the insulinotropic action of GLP-1 has been shown to be preserved in type 2 diabetic patients. All these findings support GLP-1 as an attractive alternative therapy to conventional antidiabetic agents. Many questions are still unanswered such as the causes of the incretin defect associated with type 2 diabetes. Nevertheless, the study of incretin hormones brought new concepts and fuelled food-related integrated physiology. More interesting findings are certainly forthcoming…

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