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Review

The incretins: From the concept to their use in the treatment of type 2 diabetes. Part A: Incretins: Concept and physiological functions

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Abstract

This paper briefly reviews the concept of incretins and describes the biological effects of the two incretins identified so far: the glucose-dependent insulinotropic polypeptide (GIP); and the glucagon-like peptide-1 (GLP-1). GIP is released by the K cells of the duodenum, while GLP-1 is released by the L cells of the distal ileum, in response to nutrient absorption. GIP and GLP-1 stimulate insulin biosynthesis and insulin secretion in a glucose-dependent manner. In addition, they increase beta-cell mass. GIP has a specific effect on adipose tissue to facilitate the efficient disposal of absorbed fat and, thus, may be involved in the development of obesity. GLP-1 has specific effects on pancreatic alpha cells, the hypothalamus, and gastrointestinal and cardiovascular systems. By inhibiting glucagon secretion and delaying gastric-emptying, GLP-1 plays an important role in glucose homoeostasis and, by inhibiting food intake, prevents the increase in body weight. As the metabolic effects of GIP are blunted in type 2 diabetes, this peptide cannot be used as an efficient therapy for diabetes. In contrast, GLP-1 effects are preserved at high concentrations in type 2 diabetes, making this peptide of great interest for the treatment of diabetes, a topic that will be discussed in the second part of this review.

Résumé

Les incrétines : du concept à l'utilisation thérapeutique dans le diabète de type 2. Partie A : concept et fonctions physiologiques.

Dans cet article, le concept d'incrétines est décrit brièvement ainsi que les effets biologiques des deux incrétines identifiées, le *glucose-dependent insulinotropic polypeptide* (GIP) et le *glucagon-like peptide-1* (GLP-1). Le GIP est sécrété par les cellules K du duodénum et le GLP-1 est sécrété par les cellules L de l'iléum distal, en réponse à l'absorption des nutriments. Le GIP et le GLP-1 stimulent la sécrétion d'insuline de façon glucose-dépendante et la biosynthèse d'insuline. De plus, ces deux hormones augmentent la masse des cellules ß. Le GIP a des effets spécifiques sur le tissu adipeux afin de faciliter l'utilisation la plus efficace des lipides absorbés et il pourrait ainsi être impliqué dans le développement de l'obésité. Le GLP-1 a des effets spécifiques sur les cellules alpha du pancréas, l'hypothalamus, le tractus gastrointestinal et le système cardiovasculaire. En inhibant la sécrétion de glucagon et en ralentissant la vidange gastrique, le GLP-1 joue un rôle important dans la régulation de l'homéostasie glucidique. En inhibant la prise alimentaire, le GLP-1 prévient l'augmentation de poids. Comme les effets métaboliques du GIP sont supprimés chez le diabétique de type 2, cette hormone ne peut pas être utilisée dans le traitement du diabète. En revanche, les effets du GLP-1 à forte dose sont préservés chez le diabétique de type 2, cette hormone a un grand intérêt thérapeutique pour le traitement du diabète. Cela sera discuté dans la seconde partie de cet article.

Keywords: Incretin hormones; GIP; GLP-1; Insulin secretion; Glucagon secretion; Adipose tissue; Food intake; Gastric-emptying

Mots clés : Incrétines ; GIP ; GLP1 ; Sécrétion d'insuline ; Sécrétion de glucagon ; Tissu adipeux ; Prise alimentaire ; Vidange gastrique

1. Introduction

As the aim of the present review is to discuss the use of incretins in the treatment of type 2 diabetes, it makes sense to first briefly describe the hormonal and metabolic abnormalities

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in type 2 diabetes that might benefit from such incretin treatment. Type 2 diabetes is characterized by two important defects:

- a defect of insulin action in skeletal muscle and liver (insulin resistance);
- and a bifunctional defect in pancreatic hormone secretion characterized by:
  - an incapacity of beta cells to increase insulin secretion to compensate for tissue insulin resistance [1],
  - and an increase in glucagon secretion by alpha cells despite hyperglycaemia [2].

The incapacity to compensate for insulin resistance is the result of the loss of beta-cell mass in type 2 diabetes mainly due to apoptosis of beta cells induced by glucolipotoxicity. In addition, the kinetics of insulin secretion are also markedly altered in the postabsorptive period [1]. Indeed, the early phase of insulin release is blunted in type 2 diabetes and leads to a decreased capacity of insulin to inhibit hepatic glucose production in the postprandial period. As glucagon secretion is not normally inhibited by hyperglycaemia in the postabsorptive state, increased glucagon secretion sustains liver glucose production, which explains the hyperglycaemic excursions observed after a meal. The defect in insulin action (insulin resistance) is not discussed here as it is not a direct target of incretin hormones.

2. The incretin concept

The idea that certain factors produced by the intestinal mucosa in response to nutrient ingestion are capable of stimulating the release of substances from the endocrine pancreas, thereby reducing blood glucose levels, was first introduced in the early 1900s. However, the incretin concept was developed after the introduction of insulin radioimmunoassay by Yalow and Berson [3]. It was shown that oral glucose administration is associated with a much greater increase in plasma insulin compared with the same amount of glucose given intravenously [4,5] (Fig. 1). The incretin theory was elucidated by Creutzfeld in 1979 as endocrine signals produced in the gastrointestinal tract, released by nutrients to stimulate insulin secretion in the presence of glucose [6]. This means that incretins act as amplifiers of glucose signals. This phenomenon was estimated to involve 50–70% of the total insulin secreted following oral glucose administration.

The first hormone identified was initially called ‘gastric inhibitory polypeptide’ (GIP) because of its ability to inhibit gastric secretion at pharmacological concentrations, but was later renamed ‘glucose-dependent insulinotropic polypeptide’ to reflect its incretin action at physiological concentrations. GIP is released by duodenal K cells in response to glucose and fat absorption, but it was soon recognized that GIP alone could not fully account for the incretin effect in vivo. The discovery of a second incretin hormone, glucagon-like peptide-1 (GLP-1), was made after the cloning and sequencing of the proglucagon gene [7]. GLP-1 is synthesized and released by enteroendocrine L cells in the distal ileum and colon in response to glucose, fat and protein absorption. It enhances glucose-stimulated insulin secretion [8,9].

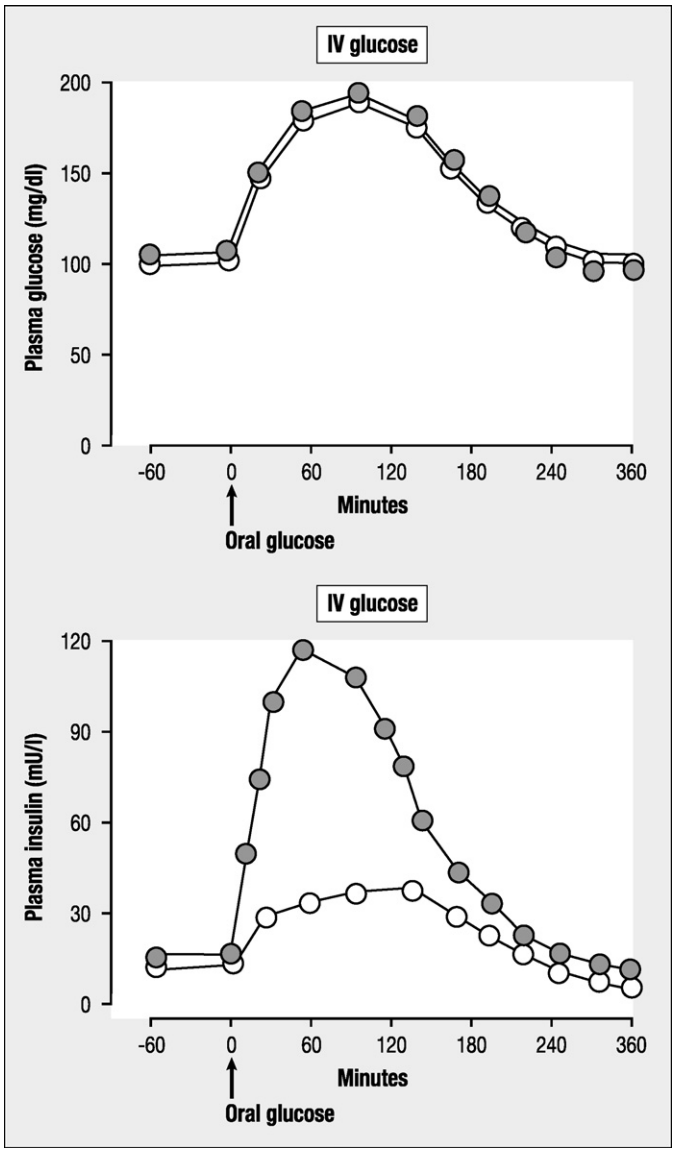

Fig. 1. The incretin effect. Different insulin concentrations in response to intravenous and oral glucose loads result in identical plasma glucose concentrations [5].

These two peptides contribute equally to the incretin effect and fully account for such activity in humans [10]. GIP is produced as an active 42 amino-acid peptide (MW 4984 Da) whereas GLP-1 is produced as an inactive 37 amino-acid peptide (MW 3298 Da) with six amino acids at the N-terminal end that are cleaved to generate the active form of GLP-1: GLP-$1_{7\text{-}37}$. This form is amidated at the C-terminal end and is the major circulating form of GLP-1 (GLP-$1_{7\text{-}36}$ amide).

3. Secretion, metabolism and clearance of incretins

Plasma concentrations of both incretins are low in the fasting state (5–10 pmol/L) and increase within 5–15 min of a meal (15–50 pmol/L). GLP-1 has two circulating molecular forms—GLP-$1_{7\text{-}37}$ and GLP-$1_{7\text{-}36}$ amide—with the latter being

more abundant in the circulation. GIP and GLP-1 are secreted in response to nutrient ingestion (carbohydrates, proteins, fats), and it is the rate of nutrient absorption rather than its mere presence in the intestine that stimulates incretin release. It is important to note that only GIP and GLP-1 secretion in response to carbohydrate absorption leads to insulin secretion (see below). Circulating levels of GIP and GLP-1 decrease rapidly as both are quickly inactivated in plasma by the enzyme dipeptidyl peptidase IV (DPPIV) [11] and by renal clearance [12]. Both are also excellent substrates for DPPIV. The circulation half-lives of the two incretins are 1–2 min for GLP-1 and 5–7 min for GIP.

3.1. GIP secretion

GIP is released by K cells in the duodenum and proximal jejunum, locations that are ideal for detecting changes in nutrient status. GIP is secreted during meals in response to nutrient ingestion, especially glucose and fat. When released in response to glucose, GIP acts rapidly on pancreatic beta cells to stimulate the release of insulin (see below). Gut K cells have features similar to those of pancreatic beta cells such as a glucose-sensing system (glucokinase) [13], which explains why the amount of GIP that enters the circulation is largely dependent upon the amount of glucose consumed. Fat absorption also stimulates GIP release, but GIP released in response to fat alone does not stimulate insulin secretion. This might reflect an insulin-independent action of GIP in fat metabolism (see below).

3.2. GLP-1 secretion

As plasma GLP-1 increases within minutes of a meal—well before digested food has transited through the gut to reach the L cells in the distal ileum and colon—a combination of endocrine and neural signals probably accounts for the rapid GLP-1 secretion. Several studies have shown that the autonomic nervous system, the neurotransmitter gastrin-releasing peptide (GRP) and acetylcholine contribute to the early phase of GLP-1 release [14]. Studies in rodents have shown that, after a meal, GIP released by K cells activates vagal afferents, leading to GLP-1 secretion through vagal efferents and enteric neurons that release acetylcholine and GRP (Fig. 2). Only oral glucose intake stimulates GLP-1 release [15] and recent experiments suggest that the action of enteral glucose could be mediated by taste receptors expressed on L cells [16]. The taste-receptor cells (T1Rs) of the lingual epithelium bind sweet compounds, and activate specific receptors coupled through the G protein 'gustducin' to specific second messenger cascades: phospholipase C and a calcium-activated channel. Duodenal L cells also express the sweet T1Rs and gustducin.

Gut L cells detect glucose through the same mechanism as that used by tongue taste cells [17,18]. Comparisons of the response to glucose directly delivered into the stomach or duodedum (to bypass the tongue) show that GLP-1 secretion is absent in gustducin-deficient mice, and that the temporal pattern of insulin secretion and glucose uptake is altered. Mice deficient in gustducin show a deficiency of GLP-1 secretion as well as of regulation of plasma glucose and insulin. In contrast, the glucose-stimulated secretion of GIP is not gustducin-dependent. Ingestion of fat, especially monounsaturated long-chain fatty acids, also stimulates GLP-1 release by L cells [14]. It has been recently reported that fatty acids bind a G protein-coupled receptor, GPR119, which is expressed in L cells and activates GLP-1 secretion [19]. Agonists of GPR119 trigger GLP-1 secretion by L cells and improve glucose homoeostasis in animal models [20]. However, a better understanding of the pathways underlying GLP-1 secretion is necessary to develop approaches by which the levels of this important insulinotropic hormone can be enhanced in type 2 diabetic patients.

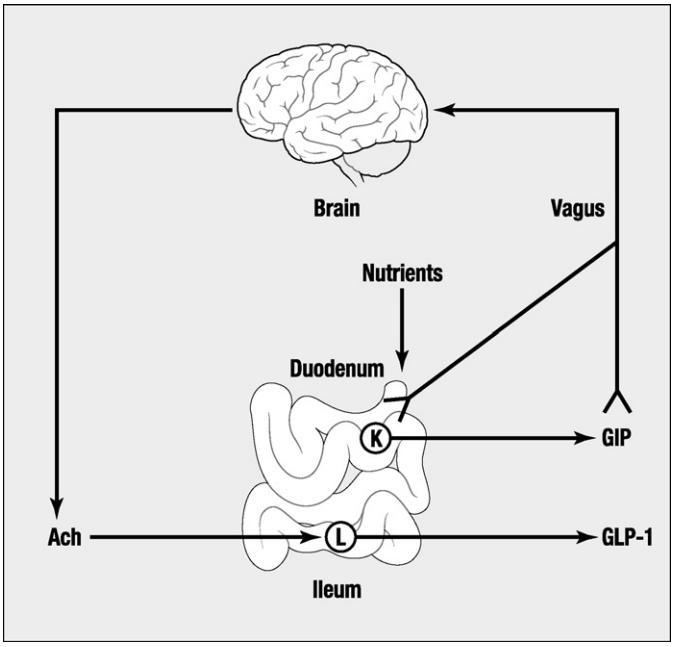

Fig. 2. Regulation of GLP-1 secretion by ingested nutrients. After a meal, nutrients in the duodenum activate a proximal neuroendocrine loop, which stimulates GLP-1 secretion from L cells in the ileum. In rodents, GIP released by K cells activates vagal afferent fibres, which, in turn, trigger GLP-1 secretion through vagal efferent fibres and enteric neurons that release acetylcholine (Ach) and gastrin-releasing peptide (GRP) [14].

4. Biological actions of incretins

Following their release from the gut, GIP and GLP-1 circulate in the blood to reach their target cells and bind to specific G protein-coupled receptors and activate their signaling pathways. The GIP receptor is predominantly expressed in islet beta cells and, to a lesser extent, in adipose, bone and brain tissues. In contrast, the GLP-1 receptor is expressed in the alpha and beta cells of the islets and in peripheral tissues, including the central and peripheral nervous system, heart, kidney, lung and gastrointestinal tract (Fig. 3).

In the present review, only the metabolic effects of incretins are discussed. What are not addressed are the effects of GIP on proliferation of progenitor cells in the brain and behavioural modifications, decreased bone resorption and increased bone formation, and the effect of GLP-1 on brain neuroprotection, learning and memory, which are reviewed elsewhere [21,22].

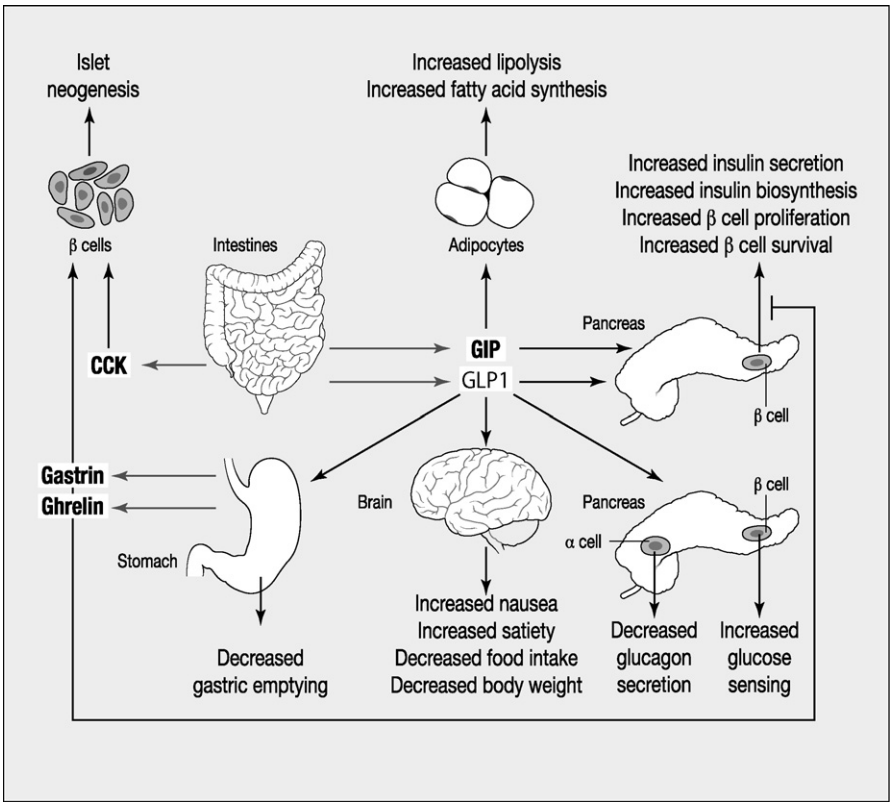

Fig. 3. Actions of gastrointestinal hormones on key tissues in glucose homoeostasis. Both GIP and GLP-1 promote insulin biosynthesis, insulin secretion and islet beta-cell survival. GLP-1 exerts additional actions, including inhibition of glucagon secretion and gastric-emptying, and induction of food intake. GIP has a direct effect on adipocytes coupled to energy storage. In contrast, CCK and gastrin do not regulate plasma glucose levels, but could be important for stimulation of islet neogenesis [7] (from ref. [7], with permission from the American Society for Clinical Investigation).

The physiological importance of endogenous GIP and GLP-1 for glucose homoeostasis has been investigated in studies of receptor antagonists and gene-knockout mice. Acute suppression of GIP and GLP-1 was found to lower insulin secretion and increase plasma glucose following a glucose tolerance test in mice. Mice with inactivated GIP or GLP-1 receptors have defective glucose-stimulated insulin secretion and impaired glucose tolerance [23,24]. GLP-1, but not GIP, is essential for the control of fasting glycaemia, as genetic disruption of GLP-1 receptors has led to fasting hyperglycaemia in animal studies.

4.1. Effects of incretins on the endocrine pancreas

Activation of both incretin receptors on pancreatic beta cells leads to rapid increases in intracellular cyclic AMP (cAMP) and calcium, followed by insulin exocytosis in a glucose-dependent manner. More sustained incretin-receptor signalling is associated with activation of cAMP-dependent protein kinase A (PKA), induction of gene transcription, enhanced levels of insulin biosynthesis and stimulation of beta-cell proliferation [25]. Both GIP and GLP-1 receptor activation also promote resistance to apoptosis and enhanced beta-cell survival [22]. GLP-1 receptors also inhibit glucagon secretion, gastric-empting and food intake, and promote enhanced glucose disposal through neural mechanisms [26]. These actions contribute to glucoregulatory control. The inhibitory effect of GLP-1 on glucagon secretion is also glucose-dependent so that the counter-regulatory release of glucagon in response to hypoglycaemia is fully preserved [27].

4.1.1. Effects of incretins on insulin biosynthesis and secretion

The primary function of GIP and GLP-1 is to enhance glucose-dependent insulin secretion. The mechanisms involved are overlapping and include an increase in intracellular cAMP, inhibition of ATP-dependent potassium (K-ATP) channels, an increase in intracellular calcium and stimulation of exocytosis. Incretins also upregulate insulin-gene transcription and biosynthesis.

4.1.1.1. Effects of GIP on insulin biosynthesis and secretion. The dominant action of GIP is stimulation of glucose-dependent insulin secretion, mediated through the increase in intracellular cAMP and inhibition of K-ATP channels that, together, induce beta-cell exocytosis (Fig. 4). GIP also promotes insulin biosynthesis.

The physiological importance of GIP as an incretin hormone is highlighted when GIP receptors are absent. Mice deprived of GIP receptors show impaired oral glucose tolerance and defective glucose-induced insulin secretion [23,28,29]. However, as the glucose intolerance found in this experimental model was not severe, it was concluded that GIP is not a unique incretin

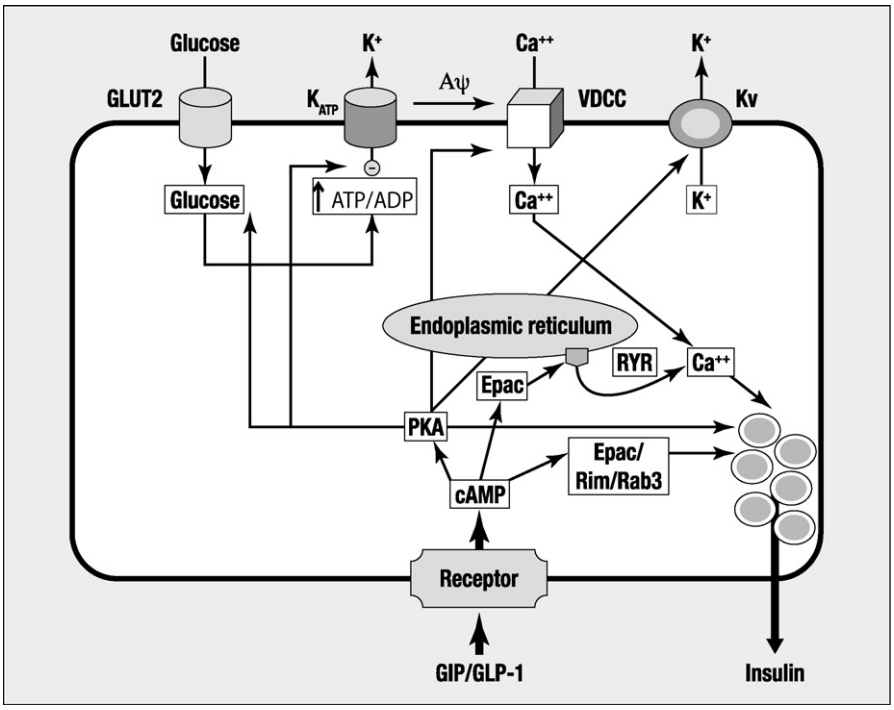

Fig. 4. GIP/GLP-1 receptor signalling and regulation of glucose-induced insulin secretion. Glucose induces insulin secretion by a signalling pathway involving glucose uptake via the glucose transporter GLUT2. Glucose metabolism increases the ATP/ADP ratio, which induces closure of the K+/ATP-dependent channel, depolarization of the plasma membrane, opening of the voltage-dependent Ca++ channel (**VDCC**) and closure of the voltage-dependent K+ channel (**Kv**). Calcium entry into beta cells induces insulin granule exocytosis. On binding to their specific receptors, GIP/GLP-1 have similar signalling pathways that activate adenylate cyclase and increase intracellular cyclic AMP (**cAMP**) levels. The effects of cAMP are then mediated by two ubiquitously expressed intracellular cAMP receptors: the classic protein kinase A (**PKA**)/cAMP-dependent protein kinase; and the recently discovered exchange protein directly activated by cAMP, (**Epac**)/cAMP-regulated guanine nucleotide exchange factor. Protein kinase phosphorylates different targets (**GLUT2**, **K+/ATP** channel, **VDCC**, **Kv**). Epac (**PKA**) stimulates the release of calcium from the endoplasmic reticulum by ryanodin (**RYR**) receptors and stimulates insulin granule exocytosis.

hormone and that other insulinotropic agents are also secreted to compensate for the lack of GIP receptor activation. Studies of mice lacking both GIP and GLP-1 receptors revealed an additive effect of GIP and GLP-1 to incretin activity [30].

4.1.1.2. Effects of GLP-1 on insulin biosynthesis and secretion. The original physiological role ascribed to GLP-1 was to stimulate insulin secretion in a glucose-dependent manner in both animals and humans [8,9]. GLP-1 also increases transcription of the gene coding for insulin and the biosynthesis of insulin by mechanisms that involve pathways that depend on, or are independent of, both cAMP and PKA, as well as pathways that increase intracellular calcium concentrations (Fig. 4). GLP-1 also improves beta-cell function by increasing expression of sulphonylurea receptors and inwardly rectifying K+ channels in beta cells. The physiological importance of endogenous GLP-1 has been demonstrated using GLP-1 receptor antagonists ($exendin_{9\text{-}39}$) and GLP-1-receptor-deficient mice. Mice lacking the GLP-1 receptors show fasting hyperglycaemia and abnormal glucose excursions with significantly reduced insulin secretion after a glucose load [31].

4.1.2. Effects of GLP-1 on glucagon secretion

GLP-1 also inhibits glucagon secretion from alpha cells after binding to its specific receptors [32] through a mechanism that has yet to be fully identified. This effect is glucose-dependent [27]. As the ability of GLP-1 to lower plasma glucose in type 1 diabetics without residual beta-cell function is retained, this indicates that a paracrine inhibitor of insulin secretion is not involved [33]. GLP-1 could inhibit glucagon secretion via stimulation of somatostatin secretion as delta cells contain specific GLP-1 receptors [34]. The cellular mechanisms are believed to involve an increase in cAMP/PKA, closure of K-ATP channels, membrane depolarization, inactivation of ion channels and reduction of intracellular calcium.

4.1.3. Effects of incretins on beta-cell mass

4.1.3.1. Effects of GIP on beta-cell mass. GIP works in synergy with glucose to stimulate beta-cell proliferation and improve survival of pancreatic beta cells. The proliferative action of GIP includes activation of cAMP/PKA, PKA/CREB and MAP kinase pathways [35–37] (Fig. 5). GIP also activates antiapoptotic pathways via the phosphatidylinositol 3-kinase (PI3-kinase)/protein kinase B (PKB) pathway. GIP activates phosphorylation of PKB and nuclear exclusion of FOXO1, resulting in decreased expression of the proapoptotic gene *BAX* and upregulation of the antiapoptotic gene *BCL2* [38].

4.1.3.2. Effects of GLP-1 on beta-cell mass. In animal studies, GLP-1 promotes the proliferation and neogenesis of pancreatic beta cells, and reduces beta-cell apoptosis [39,40]. The signal transduction pathway whereby GLP-1 mediates its proliferative

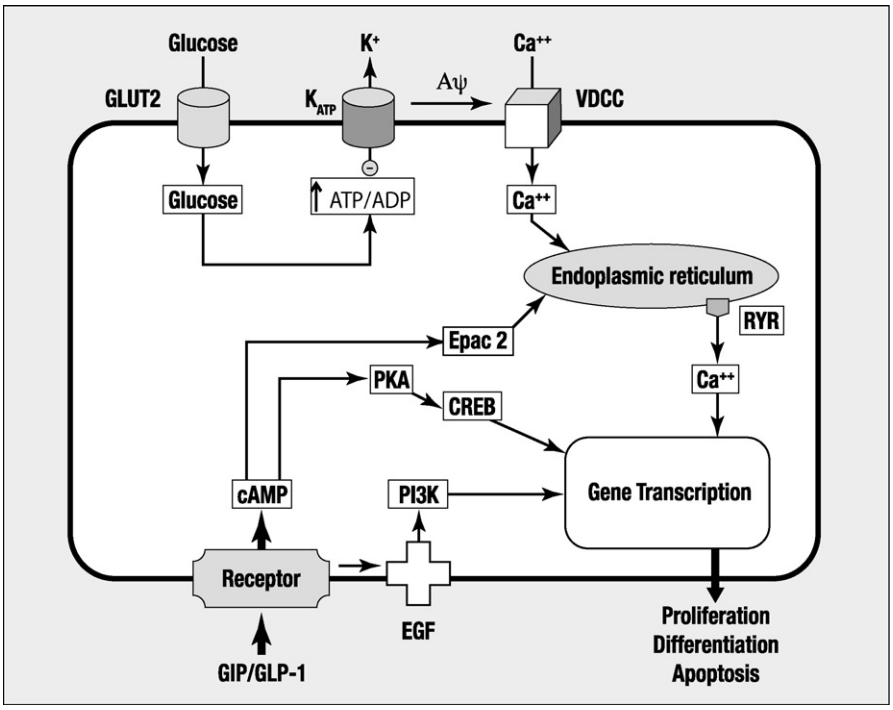

Fig. 5. GIP/GLP-1 receptor signalling and regulation of pancreatic beta-cell mass/function. On binding to their specific receptors, GIP/GLP-1 have similar signalling pathways: both activate adenylate cyclase and cyclic AMP (**cAMP**) downstream effectors (protein kinase A [**PKA**] and **Epac**). PKA increases cAMP response element-binding protein (**CREB**) transcriptional activity and upregulates insulin receptor substrate 2 (IRS2) expression. In addition, the GLP-1 receptor transactivates the epidermal growth factor (**EGF**) receptor, which activates phosphatidyl inositol 3-kinase (**PI3**-kinase) and its downstream targets which, in turn, stimulate proliferation and differentiation of beta cells and inhibits beta-cell apoptosis, thereby regulating beta-cell mass [40].

effects involves PI3-kinase, EGF receptor transactivation, MAP kinase and PKCz [41,42] (Fig. 5). GLP-1 also activates a transcriptional programme that is critical for cell survival. PDX1, FOXO1 and IRS2 have been identified as downstream targets for GLP-1-dependent cytoprotection of beta cells [43,44]. GLP-1 also reduces the expression of proapoptotic genes and prevents glucotoxicity and lipotoxicity through a mechanism involving PKB/Akt [45,46].

5. Effects of GIP on adipose tissue

GIP receptors are expressed on adipocytes and can mediate a wide variety of actions on adipocyte biology [47]. Studies in knockout mice genetically deprived of GIP receptors strongly implicate GIP in the regulation of body weight. GIP receptor-knockout mice are resistant to the development of diet-induced obesity [48]. Furthermore, GIP receptor-deficient *ob/ob* mice have a 40% reduction in body weight, and plasma lipids such as triglycerides, free fatty acids (FFA) and cholesterol [48]. Moreover, energy expenditure was increased following high-fat feeding in GIP receptor-deficient mice, indicating that inhibition of the GIP signal results in reduction of obesity, obesity-related hyperglycaemia and dyslipidaemia.

GIP released in response to fat intake could have an effect on fat metabolism [47]. GIP receptors have been found in adipocytes, and it has been reported that GIP promotes chylomicron-triglyceride clearance from the circulation [49] by increasing the activity of lipoprotein lipase [50]. Activation of lipoprotein lipase by GIP in adipocytes is mediated by phosphorylation of PKB, and reductions in phosphorylated LKB1 and AMP-activated protein kinase (AMPK) [51]. The FFA released by triglyceride hydrolysis can be taken up by adipose tissue to be stored. GIP stimulates fatty-acid synthesis and their incorporation into triglycerides. Therefore, GIP facilitates the efficient disposal of absorbed fat.

6. Effects of GLP-1 on the gastrointestinal system

GLP-1 exerts inhibitory effects on gastrointestinal (GI) secretion and motility and, in particular, on gastric-emptying [52]. Administration of GLP-1 at physiological doses in healthy volunteers results in a dose-dependent slowing of gastric-emptying and glucose absorption, both of which participate in the subsequent reduction of postprandial plasma glucose concentrations [52]. This suggests that GLP-1 participates in the 'ileal brake' phenomenon by which nutrients in the distal part of the small intestine induce a reduction in upper intestinal motility and secretory activity. The actions of GLP-1 on GI motility and secretion probably involve neural-mediated mechanisms, including vago-vagal pathways.

Under physiological conditions, it is likely that the GI effects of GLP-1—such as decreased gastric secretion and slowing of gastric-emptying—are more important than its insulinotropic action [52]. In pathological conditions such as diabetes, the inhibitory effects of GLP-1 on GI motility, particularly gastric-emptying, are of special interest because they may potentially reduce postprandial glucose excursions. It has been clearly demonstrated that slowing of gastric-emptying by the amylin

analogue pramlintide reduces postprandial entry of glucose into the systemic circulation and, thus, blunts postprandial plasma glucose excursions [53]. This highlights the importance of gastric-empting in determining postprandial plasma glucose excursions. These properties of GLP-1, taken together with the strong correlation between levels of circulating GLP-1 and rate of gastric-emptying [54], have prompted some authors to suggest that the gastric-emptying actions of GLP-1 may be as or even more important than the 'incretin' actions of GLP-1, as outlined by Nauck et al. [52] and reviewed by Nauck [55].

7. Effects of GLP-1 on food intake

In the brain, GLP-1 receptors are mainly expressed in the areas responsible for the regulation of food intake [56], and the intracerebroventricular (ICV) administration of low doses of GLP-1 has resulted in the inhibition of food intake [57,58]. Peripheral administration of GLP-1 in humans enhances satiety and reduces food intake [59–62] via a mechanism that remains unclear. GLP-1 reduces caloric intake and enhances satiety, effects that are probably related to central mechanisms. ICV administration of GLP-1 significantly reduced food intake whereas the concomitant injection of the GLP-1 receptor antagonist exendin$_{9\text{-}39}$ abolished this effect [63]. Significantly reduced food intake and consequently less weight gain was also observed after systemic administration of a GLP-1 analogue in rhesus monkeys, in diabetic *db/db* mice and in Zucker diabetic fatty rats [64]. In normal subjects, the intravenous administration of GLP-1 to above physiological levels induced increased feelings of satiety as well as a reduction of food intake [59]. Similar effects were observed in obese subjects as well as in patients with type 2 diabetes [61,62]. In type 2 diabetic patients treated with a subcutaneous infusion of GLP-1 for up to six weeks, the reduction of food intake was sustained and associated with weight loss.

The exact mechanism by which peripheral GLP-1 is able to modulate food intake has yet to be completely elucidated [64]. One possibility is that peripheral GLP-1 acts on vagal afferent fibres, permitting modulation of GLP-1 neuronal transmission in the central nervous system (CNS). This hypothesis is supported by localization of GLP-1 containing neurons in the nucleus of the tractus solitarius, which projects into the thalamic and hypothalamic regions implicated in the control of food intake. Another possibility is that circulating GLP-1 directly reaches receptors located in blood–brain barrier-free areas (such as the area postrema and subfornical organ) that, in turn, relay a signal to brain nuclei involved in nutrient homoeostasis. It is also likely that inhibition of gastric-emptying mediated by GLP-1 increases the sensation of fullness and leads to stopping eating, 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 a reduced food intake has been observed even in subjects without nausea.

8. Cardiovascular effects of GLP-1

Increasing evidence suggests that GLP-1 has beneficial effects on myocardial function. GLP-1 infusion has been reported to reduce infarct size in rodent models of myocardial ischaemia [65], and to improve myocardial contractility and glucose uptake in normal and post-ischaemic hearts [66]. GLP-1 can also improve left ventricular performance and cardiac output in dilated cardiomyopathy [67]. In humans with type 2 diabetes and congestive heart failure, GLP-1 improves myocardial function [68]. Several lines of evidence suggest that the central GLP-1 system represents a regulator of sympathetic outflow leading to downstream activation of cardiovascular responses in rodents, and are consistent with previous reports demonstrating that GLP-1 receptors function as a component of neural networks mediating the CNS response [69].

9. Does GLP-1 act on peripheral tissues via a humoral or central pathway?

GLP-1 is rapidly degraded immediately after its secretion into the portal circulation so that less than 10% of intact GLP-1 reaches the endocrine pancreas, brain and gut. It is not yet clear whether or not GLP-1 acts as a hormone, or whether it activates receptors located in the portal area and activates target tissues via the nervous system.

The importance of a portal signal for the glucose-lowering effects of GLP-1 has already been demonstrated [70]. In related studies, the same authors made the intriguing observation that GLP-1$_{7\text{-}36}$ amide, but not exendin$_4$, activated afferent fibres firing from the hepatic vagal nerve and that the effect of GLP-1 was not blocked by the GLP-1 receptor-antagonist exendin$_{9\text{-}39}$ [71]. Subsequent experiments demonstrated that intraportal GLP-1 markedly increased insulin secretion and glucose clearance, and that the effects of portal GLP-1 on insulin secretion were blocked by a ganglionic blocker [72]. The portal glucose sensor represents an incompletely understood entity that contributes to the sensing of ambient circulating glucose in the hepatoportal region. The molecular identity of the portal glucose sensor remains a subject of considerable interest. A series of experiments in mice using the GLP-1 receptor-antagonist exendin$_{9\text{-}39}$ and GLP-1 receptor-deficient mice provided new evidence of a role for basal levels of portal GLP-1 in the enhanced glucose clearance seen after portal glucose entry [26]. Pharmacological or genetic disruption of GLP-1 receptor signalling completely abrogated the enhanced glucose clearance seen after portal glucose challenge. These findings expand our knowledge of GLP-1 activity, and the GLP-1 receptor now appears to work as at least one component of an integrated physiologically relevant glucose sensor.

Intraportal infusion of GLP-1 in dogs was subsequently shown to increase primarily non-hepatic glucose disposal, as demonstrated by Nishizawa et al. and Johnson et al. [73,74], wherein intraportal GLP-1 enhanced non-hepatic glucose disposal with no detectable changes in plasma levels of insulin or glucagon. Thus, several studies have shown that GLP-1, administered either intraportally or systemically, increases glucose disposal in the liver independently of insulin secretion [75]. Consistent with data reported from studies in rodents, intraportal GLP-1 also promotes glucose clearance in dogs beyond simple stimulation of insulin secretion in associa-

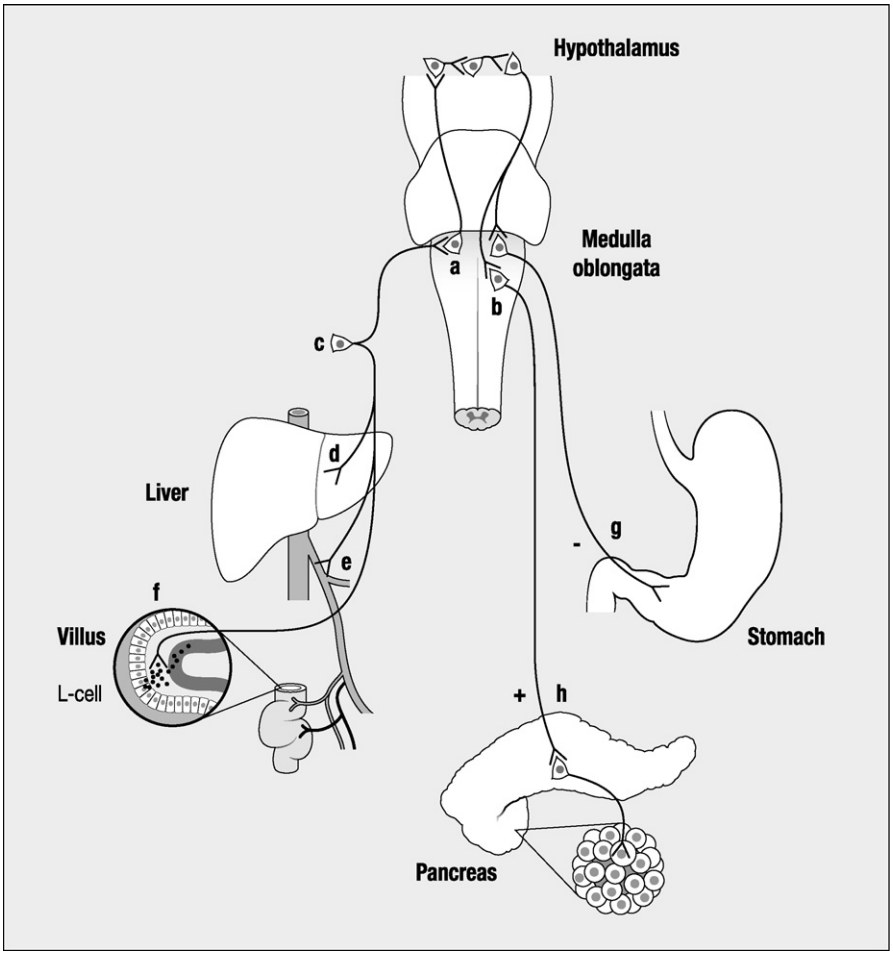

Fig. 6. The neural pathway for GLP-1 activity. GLP-1 secretion is stimulated by nutrients from L cells of the ileum. GLP-1 diffuses across the basal lumina into the lumina propria basal membrane and, on the way, activates sensory afferent neurons (**f**) originating in the nodose ganglion (**c**) that may, in turn, activate neurons of the solitary tract nucleus (**a**). The same neuronal pathway may be activated by sensory neurons in the hepatoportal area in the liver (**d**, **e**). Ascending fibres from the solitary tract neurons can generate responses in the hypothalamus, and descending impulses from the paraventricular area can activate vagal motor neurons (**b**). These neurons then send either stimulatory (**h**) or inhibitory (**g**) impulses to the pancreas and gastrointestinal tract [84] (used with permission of the authors and of the American Physiological Society).

tion with a marked induction of a counter-regulatory hormone response [76].

Can nutrients exert antidiabetic actions via enhancement of GLP-1 secretion and potentiation of the portal GLP-1 signal? Several studies have correlated an antidiabetic effect of oligofructose and reduced weight gain with an increase in portal and/or plasma levels of GLP-1—at least in rodents, as described by Cani et al. [77,78]. The central role of GLP-1 receptor signalling as an essential element in the antidiabetic actions of oligofructose has been demonstrated in mice fed a high-fat diet. The administration of the GLP-1 receptor-antagonist exendin$_{9\text{-}39}$ completely blocks the therapeutic benefits of oligofructose, and oligofructose does not exert glucose-lowering actions in GLP-1 receptor-deficient mice [79].

In addition to being secreted by the intestine, GLP-1 is also a neurotransmitter synthesized in the brainstem and transported along axonal networks to various CNS areas, including the hypothalamus. In addition, GLP-1 receptors have been found in areas of the CNS that regulate homoeostatic functions such as feeding behaviour, gastric motility, glucoregulation and cardiovascular function. Central administration of GLP-1 receptor agonists promotes satiety, decreases energy intake and leads to weight loss [57,58,80,81], which means that the physiological functions of GLP-1 in the brain are limited to the inhibition of food intake [58]. However, recent evidence has linked GLP-1 receptors in the brain to glucose homoeostasis [82]. Brain GLP-1 receptor signalling also appears to be involved in the peripheral control of glucose flux in skeletal muscle and liver, insulin sensitivity and insulin secretion, as described by Knauf et al. [83] (Fig. 6).

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