

Review

GIP and GLP-1 as incretin hormones: Lessons from single and double incretin receptor knockout mice

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Abstract

Glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are gut-derived incretins secreted in response to nutrient ingestion. Both incretins potentiate glucose-dependent insulin secretion and enhance β -cell mass through regulation of β -cell proliferation, neogenesis and apoptosis. In contrast, GLP-1, but not GIP, inhibits gastric emptying, glucagon secretion, and food intake. Furthermore, human subjects with Type 2 diabetes exhibit relative resistance to the actions of GIP, but not GLP-1R agonists. The physiological importance of both incretins has been investigated through generation and analysis of incretin receptor knockout mice. Elimination of incretin receptor action in $GIPR^{-/-}$ or $GLP-1R^{-/-}$ mice produces only modest impairment in glucose homeostasis. Similarly, double incretin receptor knockout (DIRKO) mice exhibit normal body weight and normal levels of plasma glucagon and hypoglycemic responses to exogenous insulin. However, glucose-stimulated insulin secretion is significantly decreased following oral but not intraperitoneal glucose challenge in DIRKO mice and the glucose lowering actions of dipeptidyl peptidase-IV (DPP-IV) inhibitors are extinguished in DIRKO mice. Hence, incretin receptor signaling exerts physiologically relevant actions critical for glucose homeostasis, and represents a pharmacologically attractive target for development of agents for the treatment of Type 2 diabetes.

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1. Introduction

Diabetes mellitus is a chronic disease of epidemic proportions and new treatments are required for the effective treatment of both Type 1 and Type 2 diabetes mellitus. Whereas Type 1 diabetes is characterized by β -cell failure due to autoimmune insulinitis, Type 2 diabetes arises as a result of β -cell failure often in the setting of concomitant insulin resistance. Since patients with insulin resistance do not develop hyperglycemia until the β cell is unable to meet the demand for insulin, enhancement of insulin secretion from the islet β cell is an important goal for treatment of patients with Type 2 diabetes mellitus. Current insulin secretagogues, including sulfonylureas and glitinides fre-

quently exhibit a progressive reduction in efficacy and may cause hypoglycemia in patients with Type 2 diabetes, hence there is much interest in identification of newer agents which potentiate insulin secretion in a sustained glucose-dependent manner in subjects with Type 2 diabetes.

Incretins are hormones released from the gut in response to nutrient ingestion that potentiate glucose-stimulated insulin secretion [1]. The search for incretins was prompted by the observation that administration of an oral glucose load leads to a much greater stimulation of insulin release compared to a comparable glucose challenge given intravenously [2,3]. McIntyre et al. [4] suggested that there was a humoral substance present in the gut released in response to glucose administration that stimulated the release of insulin from the endocrine pancreas. This connection between the gut and the pancreatic islets has been termed as the 'enteroinsular axis' [5] and is responsible for ~50% of postprandial insulin release [3].

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An important advance in incretin research was the isolation and characterization of glucose-dependent insulinotropic peptide (GIP). GIP is released from enteroendocrine K cells in the duodenum, primarily in response to the ingestion of glucose or fat [6,7] and potentiates insulin secretion in a glucose dependent manner [8,9]. However, GIP alone does not account fully for the incretin effect. In vivo immunoneutralization of GIP or removal of GIP from intestinal extracts did not completely eliminate the incretin effect [10,11], suggesting the presence of additional gut-derived factors with insulinotropic activity.

The cloning of the mammalian proglucagon gene in 1983 led to the identification of two novel peptides carboxyterminal to the glucagon sequence which were subsequently named glucagon-like peptides (GLP-1 and GLP-2) due to their significant amino acid identity with glucagon [12]. Initial characterization of GLP-1 bioactivity using NH₂-terminally extended GLP-1 (1-37) or GLP-1 (1-36) amide failed to demonstrate effects on blood glucose or insulin secretion [13]. However, in 1986 it was discovered that NH₂-terminally truncated GLP-1 (7-37) or GLP-1 (7-36) amide stimulated insulin secretion, islet cell cAMP formation and insulin gene expression [14–17]. Although several gut peptides and neurotransmitters exhibit incretin-like activity, evidence from experiments employing immunoneutralizing antisera, antagonists, and genetic loss-of-function studies in mice suggests that GIP and GLP-1 are the dominant peptides involved in nutrient stimulated insulin secretion and account fully for the incretin effect [18,19]. The focus of this review is on the actions of GLP-1 and GIP (Fig. 1) with special emphasis on the physiological consequences of acute or chronic loss of incretin action.

2. Incretin synthesis and secretion

The human proglucagon gene is located on the long arm of chromosome 2 [20] and consists of six exons and five introns [21]. In mammals, the proglucagon gene gives rise to a single, identical mRNA transcript that is translated and processed differently in the pancreatic islets, intestine and brain [21,22]. Relatively little is known about the regulation of intestinal proglucagon gene expression, or the regulation of GLP-1 biosynthesis in intestinal L cells. Because the enteroendocrine L cell is exposed to both the contents of the intestinal lumen and circulating hormonal factors, intestinal proglucagon synthesis and secretion is subject to modulation by both nutrient and hormonal factors [23]. The liberation of GLP-1 in the intestine but not in the pancreas is due to the tissue-specific expression of prohormone convertases (PCs); PC1/3 expressed in enteroendocrine cells is the enzyme responsible for the liberation of GLP-1 [24]. Although multiple immunoreactive forms of GLP-1 are liberated in vivo, including GLP-1 (7-37) and GLP-1 (7-36) amide, the majority of circulating GLP-1 is GLP-1 (7-36) amide [25]. GLP-1 (7-37) and GLP-1 (7-36) amide are equipotent with regard to their insulin-stimulating properties and exhibit identical half-lives [26,27].

GLP-1 is rapidly released into the circulation after ingestion of a mixed meal in both rodents and humans [28–30]. Oral administration of nutrients in humans produces a biphasic increase in plasma GLP-1, with an early peak within 15–20 min after nutrient ingestion, followed by a second peak in GLP-1 secretion approximately 1–2 h later [28,31]. As GLP-1 producing L cells reside predominantly in the distal small intestine and colon

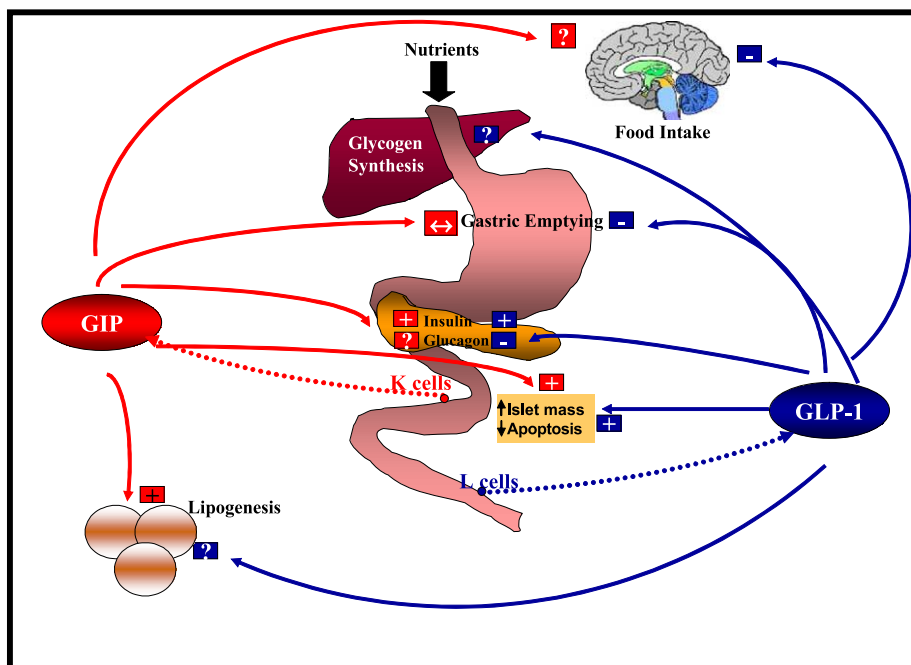


Fig. 1. Schematic representation of the overlapping and contrasting actions of the two principal incretins, GIP and GLP-1.

[32], it is unlikely that the rapid increase in plasma GLP-1 is mediated by direct action of nutrients on intestinal L cells. Thus, the existence of a proximal-distal loop has been proposed that transmits nutrient-induced stimulatory signals via neural or endocrine effectors to the distal L cell [33].

The human GIP gene is located on the long arm of chromosome 17 [34], and also contains six exons [21]. GIP is derived from a larger proGIP precursor encoding a signal peptide, an N-terminal peptide, GIP, and a C-terminal peptide [35]. The mature, bioactive 42 amino acid peptide is liberated from proGIP via posttranslational cleavage at single arginine residues that flank the peptide [35–37]. In rodents and humans, the GIP gene is expressed in the stomach, in the K cells of the intestine and in the submandibular salivary gland [35,36,38,39]. The ingestion of a carbohydrate- and fat-rich meal is a potent stimulus for the secretion of GIP [7,8]. GIP levels peak 15–30 min after oral glucose ingestion [7,8].

3. Incretin degradation and clearance

Both GLP-1 and GIP undergo rapid proteolytic cleavage by the ubiquitous serine protease, dipeptidyl peptidase-IV (DPP-IV) at their penultimate alanine residue, producing N-terminally truncated peptides incapable of stimulating insulin secretion [40,41]. The disappearance of exogenously administered GLP-1 and GIP has been studied in rodents as well as in normal and diabetic humans, using assays capable of differentiating between full-length and N-terminally truncated peptides. The half-life of exogenously administered bioactive GLP-1 is less than 2 min in rodents [41] and in normal and diabetic human subjects [42]. The half-life of infused GIP is less than 2 min in rodents [41], and ~7 min in normal human subjects, whereas Type 2 diabetic subjects exhibit a GIP half-life of ~5 min [43]. The primary route for incretin clearance appears to be the kidney [44,45].

4. GLP-1 action

4.1. The GLP-1 receptor

The GLP-1 receptor was cloned from a rat pancreatic islet cDNA library [46] and belongs to the seven-membrane spanning, G-protein coupled family of receptors, including glucagon, PACAP, VIP, GIP and secretin [47]. In humans and rodents, the GLP-1R is expressed in various tissues including the α , β , and δ cells of the islets of Langerhans, lung, stomach, heart, intestine, kidney and the brainstem, hypothalamus and pituitary [48–51]. Only a single GLP-1R has been identified, which is structurally identical in all tissues [48]. Nevertheless, the presence of functional GLP-1 receptors in peripheral tissues such as muscle, fat and liver remains controversial [49,52] and has prompted the

suggestion that a second, closely related GLP-1 receptor remains to be identified [53,54].

GLP-1 stimulates adenylate cyclase and phospholipase C and subsequent activation of PKA and PKC, respectively [16,46,49], as well as increases in cytosolic free Ca^{2+} in islet and non-islet cell lines [55,56]. Similar activities have been identified for GLP-1R agonists such as exendin-4, a 39 amino acid peptide isolated from the venom of the *Heloderma suspectum* lizard [57] which shares approximately 53% amino acid identity with mammalian GLP-1. An N-terminally truncated version of lizard exendin-4, exendin(9-39) also binds to the GLP-1R and functions as a relatively specific GLP-1R antagonist [58,59].

4.2. GLP-1 actions in the pancreas

GLP-1 exerts its insulinotropic effects primarily by elevation of levels of cAMP and activation of protein kinase A. GLP-1 may also exert its effects through cAMP-dependent PKA-independent mechanisms involving activation of guanine nucleotide exchange factors (GEFs) [60]. GLP-1 synergizes with glucose to stimulate insulin secretion through mechanisms that involve closure of ATP-sensitive K^+ channels (K_{ATP}) resulting in subsequent membrane depolarization, increases in intracellular Ca^{2+} and potentiation of Ca^{2+} induced secretion via direct effects on the β -cell exocytotic machinery [61]. The insulinotropic effects of GLP-1 and GIP are dependent on the plasma glucose concentrations. However, until recently it was not very clear how this glucose dependency was achieved. Under fasting or euglycemic conditions when the ADP/ATP ratio is high, activation of PKA results in enhancement of K_{ATP} current and minimal effects on insulin secretion [62]. However, under fed conditions when glucose metabolism results in decreased levels of ADP, activation of PKA results in inhibition of K_{ATP} current and hence, depolarization [62]. GLP-1 and GIP may also augment insulin release by inhibiting voltage dependent K^+ channels that under depolarizing conditions act to repolarize the cell [63].

GLP-1 and GIP also increase insulin gene transcription, mRNA stability and biosynthesis [16,64], thereby allowing β -cell insulin stores to recover following stimulation of insulin secretion. GLP-1 also inhibits glucagon secretion [65,66] and stimulates somatostatin secretion [66]. The increase in somatostatin secretion is mediated directly via GLP-1 receptors expressed on the somatostatin producing δ cells, whereas the inhibitory effect of GLP-1 on glucagon secretion may be direct via interaction with GLP-1 receptors on α cells or via stimulation of insulin and somatostatin secretion, both of which inhibit glucagon secretion [67].

GLP-1 exerts several actions on islet β cells in addition to its insulinotropic effects. GLP-1 confers glucose sensitivity to glucose-resistant β cells, thereby improving the ability of the β cells to sense and respond appropriately to

glucose [68]. GLP-1 administration leads to induction of proliferation and neogenesis of pancreatic cells. GLP-1 stimulates DNA synthesis [69] and induces differentiation of pluripotent pancreatic cells into insulin-secreting cells with endocrine properties [70,71]. Acute or chronic administration of GLP-1 or its long acting analogues has been shown to increase β -cell mass in normal and diabetic mice [72–74]. Treatment with GLP-1 improves the age-related decline in glucose tolerance in rats, in part by enhancing β -cell mass [75]. Exendin-4 has been shown to prevent or delay the onset of diabetes in db/db mice and reduces the severity of diabetes following streptozotocin treatment or partial pancreatectomy [76–78].

Activation of GLP-1R signaling is also coupled to inhibition of apoptosis. Concomitant administration of exendin-4 with the β -cell toxin streptozotocin attenuates β -cell apoptosis [79]. Exendin-4 also decreases cytokine-induced apoptosis in isolated murine β cells [79]. Furthermore, GLP-1 improves the viability of freshly isolated human islets, in part by down-regulation of caspase-3 and up-regulation of the anti-apoptotic protein Bcl-2 [80]. GLP-1 also improves cell survival following exposure to apoptosis-inducing agents such as streptozotocin, cytokines, fatty acids and peroxides [79,81,82].

4.2.1. Extrapancreatic actions of GLP-1 contribute to glucose homeostasis

GLP-1 inhibits gastric emptying [83] thereby attenuating the meal-associated increases in blood glucose by slowing the transit of nutrients from the stomach to the small intestine. In diabetic subjects, GLP-1 infusion produces significant decreases in meal related glycemic excursion, even without an increase in plasma insulin secretion due to potent inhibitory effects on gastric emptying [84]. The GLP-1R-dependent inhibition of gastric emptying is blocked by the antagonist exendin(9-39) [85]. GLP-1-immunoreactive nerve fibers and GLP-1 receptors are localized in regions of the brain known to regulate energy homeostasis [86,87]. Acute intracerebroventricular administration of GLP-1 produces a transient reduction in food intake in rodents [88], whereas chronic peripheral administration of GLP-1R agonists promotes satiety, weight loss and suppresses energy intake in rodents [89–91] and in humans [92–94]. The inhibitory effects of GLP-1 on food intake may involve direct or indirect effects on hypothalamic feeding centers, and may be mediated in part through inhibition of gastrointestinal motility. GLP-1 actions on food intake may also be due in part to induction of a conditioned taste aversion response and activation of CNS aversive signaling pathways [95–97].

The physiological importance of GLP-1 signaling has been studied using both GLP-1R antagonists such as exendin(9-39) and GLP-1R^{-/-} mice. The ability of exendin(9-39) to reduce postprandial insulin levels and deteriorate glucose tolerance led to the conclusion that GLP-1 is a physiologically relevant incretin *in vivo*. Infusion of

exendin(9-39) into rodents, baboons and humans produces an increase in fasting glucose and glycemic excursion after oral glucose challenge in association with decreased circulating levels of glucose stimulated insulin [98–101]. Administration of exendin(9-39) also results in impaired glycemic excursion in mice after intraperitoneal glucose challenge [101].

4.2.2. The GLP-1R^{-/-} mouse

Mice with a targeted disruption of the GLP-1R gene have been used as a tool to understand the biological importance of GLP-1. GLP-1R^{-/-} mice exhibit mild fasting hyperglycemia and glucose intolerance after an oral glucose challenge in association with reduced glucose-stimulated insulin secretion [102]. GLP-1R^{-/-} mice also exhibit abnormal glycemic excursion following intraperitoneal glucose challenge demonstrating that GLP-1 is important for clearance of the glucose load, irrespective of the site of glucose entry into the circulation [102]. Despite evidence that GLP-1 is a potent inhibitor of short-term food intake, GLP-1R^{-/-} mice in the CD1 genetic background exhibited normal body weight and food intake [102]. Surprisingly, intact GLP-1R signaling was not required for maintenance of glucose competence in pancreatic β cells as glucose-induced insulin release was preserved in intact isolated islets from GLP-1R^{-/-} mice [103]. Under fasting conditions, no significant changes in fasting insulin mRNA and content were observed [104], whereas under fed conditions, a modest reduction in insulin mRNA and pancreatic insulin content was detected in GLP-1R^{-/-} mice [105]. Although GLP-1 inhibits glucagon secretion and has been postulated to directly regulate peripheral glucose disposal, GLP-1R^{-/-} mice exhibit normal fasting and postprandial levels of glucagon and display normal whole-body glucose utilization [104].

The relatively modest perturbations in glucose homeostasis in GLP-1R^{-/-} mice have fostered a search for compensatory mechanisms that modify the phenotype of GLP-1R deficiency. Both GIP secretion and GIP action (enhanced GIP-stimulated cAMP production and insulin release) are up-regulated in GLP-1R^{-/-} mice [105]. Islets from GLP-1R^{-/-} mice also exhibit abnormalities in basal and glucose-stimulated cytosolic Ca²⁺ [106]. Despite evidence implicating GLP-1R signaling as an important pathway for regulating β -cell proliferation and survival, β -cell mass is normal in GLP-1R^{-/-} mice. However, GLP-1R^{-/-} mice exhibit abnormalities in islet number, islet size and distribution of α cells [107]. Although ob/ob:GLP-1R^{-/-} mice exhibit a robust compensatory increase in β -cell mass and marked up-regulation of insulin gene expression [108], GLP-1R^{-/-} mice exhibit increased susceptibility to streptozotocin induced apoptosis [79]. Furthermore, GLP-1R^{-/-} mice exhibit a greater deterioration in glucose tolerance following partial pancreatectomy in association with a decrease in the extent of β -cell regeneration [109]. These studies suggest that although GLP-1R signaling may not always be essential for control of β -cell mass, elimination of GLP-

1R signaling renders the β cell more susceptible to external injury.

To determine the contribution of specific genetic backgrounds to the phenotype of GLP-1R deficiency, we backcrossed GLP-1R^{-/-} mice for five generations into the C57 BL/6 background. In contrast to findings in CD1 GLP-1R^{-/-} mice, GLP-1R^{-/-} mice in the C57BL/6 background do not exhibit fasting hyperglycemia [110]. Although GLP-1R^{-/-} mice exhibit small but significant increases in food intake over a 24-h time period [110], GLP-1R^{-/-} mice in the C57BL/6 background are not obese and paradoxically exhibit a trend towards lowered body weight. These findings indicate that the genetic background may modify the specific phenotype observed as a consequence of loss of incretin receptor signaling.

5. GIP action

5.1. The GIP receptor

The GIP receptor was originally cloned from a rat cerebral cortex cDNA library [111] and is expressed in pancreas, stomach, small intestine, adipose tissue, adrenal cortex, lung, pituitary, heart, bone, vascular endothelium and several regions of the brain [111,112]. The GIP receptor belongs to the same GPCR superfamily as GLP-1 [47] and is positively coupled to activation of adenylate cyclase, and increases in intracellular Ca²⁺ [56,113,114].

5.2. GIP actions in the pancreas

GIP is released from intestinal K cells and potentiates glucose-stimulated insulin secretion. The mechanisms by which GIP stimulates insulin secretion are similar to those identified for GLP-1 and include elevation of cAMP, inhibition of K_{ATP} channel and increases in intracellular Ca²⁺. The signaling pathways that mediate the insulinotropic actions of GIP include PKA-dependent and PKA-independent mechanisms [60]. Administration of GIP immunoneutralizing antisera to rats and mice attenuates glucose-dependent insulin secretion after oral glucose loading [101,115].

While the actions of GLP-1 and GIP on the β cell are quite similar, they exert differential actions on other islet cell types. Unlike GLP-1, GIP exhibits glucagonotropic effects under euglycemic conditions in human subjects [116]. GIP also promotes β -cell proliferation and inhibits apoptosis in vitro [117–119]. The signaling pathways that mediate the proliferative and anti-apoptotic actions of GIP on β cells include activation of cAMP/PKA, MAPK and PI3K [117–119]. However, unlike GLP-1 there is a paucity of data demonstrating that GIP increases β -cell mass by stimulating proliferation and inhibiting apoptosis in vivo. Although mice lacking DPP-IV are resistant to streptozotocin-induced β -cell damage [120] and administration of a DPP-IV

inhibitor to streptozotocin-treated rats results in expansion of β -cell mass [121], the relative contributions of GLP-1 versus GIP for promotion of β -cell mass in these experimental paradigms remain unclear.

5.3. Extrapancreatic effects of GIP

Unlike GLP-1, GIP does not inhibit gastric emptying in humans [122] but does up-regulate intestinal hexose transport [123]. GIP is an anabolic hormone for adipocyte lipid metabolism and stimulates lipoprotein lipase activity [124], thereby promoting fat storage. GIP also promotes fatty acid incorporation into adipose tissue [125]. GIP infusion promotes triglyceride clearance from the circulation in dogs [126] and inhibits the lipolytic effect of glucagon on adipocytes [127,128]. Although the GIPR is expressed in various regions of the brain, the actions of GIP in the central nervous system remain uncertain.

5.4. GIPR^{-/-} mice

Evidence for the importance of GIPR signaling for glucose homeostasis and lipid metabolism is derived from studies in GIPR^{-/-} mice. GIPR^{-/-} mice exhibit mild glucose intolerance in response to an oral glucose challenge in association with reduced levels of glucose-stimulated insulin secretion [129]. However, in contrast to GLP-1R^{-/-} mice, GIPR^{-/-} mice exhibit normal fasting glucose and normal glycemic excursion in response to an intraperitoneal glucose challenge [129]. These findings suggest that the role of GIP is primarily restricted to that of an incretin. Studies in perfused pancreata and isolated islets demonstrate that glucose competence is preserved in GIPR^{-/-} mice [130]. Furthermore, these mice exhibit no significant changes in insulin sensitivity [130]. Despite evidence that GIPR signaling is coupled to proliferation and inhibition of apoptosis in vitro, islets from GIPR^{-/-} mice paradoxically exhibit an increase in β -cell area [130]. Islets from GIPR^{-/-} mice also exhibit increased sensitivity to exogenous GLP-1 [130]. Although GIP has no direct effects on food intake or satiety, the GIPR^{-/-} mouse exhibits resistance to diet-induced obesity after months of high fat feeding [131]. Furthermore, when GIPR^{-/-} mice were crossed with ob/ob mice, diet-induced obesity was attenuated in the double transgenic ob/ob:GIPR^{-/-} mice [131].

5.5. GLP-1R^{-/-}:GIPR^{-/-} (DIRKO) mice

As single incretin receptor knockout mice exhibit comparatively modest phenotypes (Table 1), potentially due in part to compensation by the complementary incretin, double incretin receptor knockout (DIRKO) mice were generated to elucidate the physiological consequences arising following genetic disruption of both GIP and GLP-1 receptor genes. DIRKO mice exhibit mild disturbances in food intake over 24-h time period [110], and exhibit a trend

Table 1
Essential actions revealed in GLP-1R^{-/-} and GIPR^{-/-} mice

	GLP-1R ^{-/-}	GIPR ^{-/-}
Fasting glucose	Abnormal	Normal
Glucose-dependent insulin secretion	Abnormal	Abnormal
β-Cell signal transduction	Abnormal	Abnormal
Glucagon secretion	Normal	Normal
Gastric emptying	Normal	NYD
Food intake	Normal	Normal
Body weight	Normal	Normal
Islet size	Abnormal	Normal
β-Cell+neuronal apoptosis	Abnormal	NYD

NYD=not yet demonstrated.

towards lowered body weight with increasing age. Although exogenous GLP-1 and GIP are potential regulators of glucagon secretion, no significant differences were observed in levels of circulating plasma glucagon in the fasting or fed state [110]. Consistent with the physiological importance of incretin hormones in stimulating glucose-induced insulin secretion, DIRKO mice exhibit significantly impaired glycemic excursion compared to wild-type and single incretin receptor knockout mice, and decreased levels of circulating insulin after oral glucose challenge [110,132]. Similar to GLP-1R^{-/-} mice, DIRKO mice also exhibit abnormal glycemic excursion after intraperitoneal glucose loading [110,132]. In islets from single incretin receptor knockout mice, glucose-stimulated insulin secretion is preserved [103,105,129,130]; however, DIRKO islets exhibit a modest insulin secretory defect depending in part on the specific experimental paradigm [110,132].

In light of the therapeutic potential of enhancing incretin action for the treatment of Type 2 diabetes, DPP-IV inhibition has emerged as a novel strategy for potentiating incretin action in vivo [133]. Administration of DPP-IV inhibitors prior to an oral glucose challenge improves glycemic excursion in association with increased levels of circulating insulin in wild-type and single incretin receptor knockout mice [110]. However, administration of DPP-IV inhibitors has no significant effect on glucose or insulin secretion in DIRKO mice [110]. These findings suggest that the glucose lowering properties of DPP-IV inhibitors are primarily mediated by enhancing incretin action following acute DPP-IV inhibitor administration. However, whether more chronic administration of DPP-IV inhibitors to DIRKO mice may improve glucose tolerance and β-cell function remains to be determined.

6. Summary

Considerable progress has been made in the elucidation of the physiological actions of GIP and GLP-1 with special reference to the islet β cell. In contrast, a number of important questions regarding incretin action remain unanswered. The importance of direct versus indirect incretin action, in part through the vagus nerve, for control of insulin

secretion remains unclear. The physiological relevance of incretins for physiological actions independent of insulin secretion is an area of active investigation. For example, GIP actions in bone, adipose tissue, and the central nervous system require more careful analysis (Fig. 1). Finally, the surprisingly modest phenotype of mice with single or double incretin receptor gene disruption suggests the existence of compensatory factors which modify the deficiency of GLP-1 and GIP action in vivo. The identification of these compensatory pathways, and further delineation of physiological actions and therapeutic potential of incretin mimetics for the treatment of Type 2 diabetes remain important topics for future research studies.

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