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Minireview: Glucagon-Like Peptides Regulate Cell Proliferation and Apoptosis in the Pancreas, Gut, and Central Nervous System

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Gut peptides exert diverse effects regulating satiety, gastrointestinal motility and acid secretion, epithelial integrity, and both nutrient absorption and disposal. These actions are initiated by activation of specific G protein-coupled receptors and may be mediated by direct or indirect effects on target cells. More recent evidence demonstrates that gut peptides, exemplified by glucagon-like peptides-1 and 2 (GLP-1 and GLP-2), directly regulate signaling pathways coupled to cell proliferation and apoptosis. GLP-1 receptor activation enhances β-cell proliferation and promotes islet neogenesis via activation of pdx-1 expression. The proliferative effects of GLP-1 appear to involve multiple intracellular pathways, including stimulation of Akt, activation of protein kinase Cζ, and transactivation of the epidermal growth factor receptor through the c-src kinase. GLP-1 receptor activation also promotes cell survival in β-cells and neurons via increased levels of cAMP leading to cAMP response element binding protein activation, enhanced insulin receptor substrate-2 activity and, ultimately, activation of Akt. These actions of GLP-1 are reflected by expansion of β-cell mass and enhanced resistance to β-cell injury in experimental models of diabetes *in vivo*. GLP-2 also promotes intestinal cell proliferation and confers resistance to cellular injury in a variety of cell types. Administration of GLP-2 to animals with experimental intestinal injury promotes regeneration of the gastrointestinal epithelial mucosa and confers resistance to apoptosis in an indirect manner via yet-to-be identified GLP-2 receptor-dependent regulators of mucosal growth and cell survival. These proliferative and antiapoptotic actions of GLP-1 and GLP-2 may contribute to protective and regenerative actions of these peptides in human subjects with diabetes and intestinal disorders, respectively. (*Endocrinology* 145: 2653–2659, 2004)

A NUMBER OF gut peptide hormones exhibit diverse biological actions that include not only the acute regulation of metabolism, but also the growth and survival of cells in the gastro-enteropancreatic-brain axis. The dual proliferative and antiapoptotic action of several of these hormones has focused attention on understanding how a single peptide regulates distinct pathways coupled to either growth or cytoprotection. The focus of this review is on two related intestinal hormones, glucagon-like peptide-1 (GLP-1) and GLP-2, that play key roles in the regulation of nutrient homeostasis, as well in the proliferative and antiapoptotic responses of the pancreatic β-cell and the intestinal epithelial cell, respectively.

GLP-1

Glucose-dependent insulinotropic peptide (GIP) and GLP-1 are the major physiological incretins, intestinal hormones released in response to nutrient ingestion that stimulate glucose-dependent insulin secretion (1). GIP is a 42-amino acid peptide released from K cells that are localized predominantly in the duodenum. Although early reports demonstrated an inhibitory effect of this hormone on acid secretion, subsequent studies established a predominant role for GIP as an incretin. The structurally related hormone, GLP-$1^{7-36NH2}$, is released from L cells in the distal ileum and colon and also serves important roles as an incretin; GLP-1 not only stimulates insulin secretion, but also inhibits gastric emptying and glucagon secretion (2). Based upon studies with antagonists in both humans and rodents, GLP-1 and GIP are believed to account for almost the entire incretin effect that facilitates disposal of ingested nutrients. Consistent with these findings, mice with null mutations in either the GLP-1 or GIP receptor genes exhibit impaired glucose tolerance (3, 4). Similarly, experiments preventing GLP-1 and GIP degradation through the use of dipeptidyl peptidase IV (DPP-IV) inhibitors, studies of degradation-resistant peptide analogs or analysis of rodents with null mutations in the DPP-IV gene, have demonstrated that improved glucose tolerance is consistently observed in association with increased levels GLP-1 or GIP (2, 5). Accordingly both GLP-1 and GIP have been proposed for the treatment of patients with type 2 diabetes (T2DM) (2). However, T2DM is associated with resistance to the actions of GIP (6); hence, current clinical trials are focused on examining the therapeutic potential of degradation-resistant GLP-1 analogs, or DPP-IV inhibitors for the treatment of T2DM (2). Indeed, these approaches have been shown to reduce glycemia acutely, as well as to lower HbA1c levels in 4- to 12-wk clinical studies (7–9). Notwithstanding these emerging clinical results, experimental studies have elucidated additional biological actions for GLP-1

Abbreviations: CCK, Cholecystokinin; DPP-IV, dipeptidyl peptidase IV; EGF, epidermal growth factor; EGFR, EGF receptor; GIP, glucose-dependent insulinotropic peptide; GLP, glucagon-like peptide; GLP-1R, GLP-1 receptor; GLP-2R, GLP-2 receptor; GPCR, G protein-coupled receptor; T2DM, type 2 diabetes.

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and GIP, as trophic factors for the β-cell. As β-cell mass is reduced by up to 60% in patients with T2DM (10, 11), there exists great interest in the potential for new therapeutic agents simultaneously capable of lowering HbA1c and expanding functional β-cell mass.

GLP-1 and the regulation of β-cell mass: in vivo studies

Acute or chronic administration of either GLP-1 or of its degradation-resistant analogs increases β-cell mass by up to 2-fold in normal or diabetic mice (Table 1) (12–14). Similar studies have demonstrated that GLP-1 receptor (GLP-1R) agonists enhance β-cell mass in aged, glucose-intolerant rats (15), although the extent to which GLP-1R agonists increase islet mass may be dependent, in some but not all animal models, on the concurrent metabolic milieu and pre-existing β-cell mass (14, 16, 17). Furthermore, GLP-1R agonists such as exendin-4 also prevent or delay the development of diabetes in db/db mice and Goto-Kakizaki rats and reduce the severity of diabetes in rats following partial pancreatectomy or neonatal administration of streptozotocin; all of these changes occur in association with enhancement of β-cell mass (17–20). Similarly, administration of exendin-4 in the neonatal period to rats following induction of experimental intrauterine growth retardation is associated with a reduced incidence of diabetes, increased β-cell proliferation, and expansion of β-cell mass in adult animals (21). However, it is noted that persistent transgenic expression of the potent GLP-1 receptor agonist, exendin-4, is not associated with perturbations in β-cell mass in mice (22), consistent with the likelihood that multiple factors influence the GLP-1R-dependent regulation of β-cell mass (23).

In contrast with data obtained with GLP-1, much less is known about the importance of GIP for preservation or expansion of β-cell mass. Although administration of DPP-IV inhibitors increases the levels of both GLP-1 and GIP in association with expansion of β-cell mass (24), and DPP-IV-deficient mice exhibit resistance to streptozotocin-induced β-cell damage (25), the relative contributions of GIP *vs.* GLP-1 to islet growth remain unclear. GIPR−/− mice exhibit a paradoxical increase in β-cell mass (26); however, whether GIP analogs stimulate expansion of β-cell mass in diabetic rodents has not yet been determined.

Analysis of whether GLP-1 action is essential for one or more aspects of physiological β-cell growth has also been examined, through experiments employing mice with an inactivating mutation in the GLP-1R gene. GLP-1R−/− mice exhibit normal β-cell mass yet display a shift toward more medium and small islets, and a significant reduction in the numbers of large islets (27). The importance of endogenous GLP-1R action for the β-cell response to insulin resistance has also been studied, in double transgenic ob/ob:GLP-1R−/− mice. Marked β-cell hyperplasia and increased insulin biosynthesis accompanies the development of diabetes in leptin-deficient ob/ob mice. Remarkably, ob/ob:GLP-1R−/− mice exhibit the same degree of islet hyperplasia and compensatory increases in proinsulin gene expression compared with ob/ob mice with intact GLP-1R signaling (28). In contrast, GLP-1R−/− mice exhibit more marked hyperglycemia and a reduced capacity for β-cell regeneration following experimental pancreatectomy (23). Hence, the relative importance of GLP-1R action for β-cell growth and regeneration appears dependent upon the specific experimental setting.

Mechanism of action of GLP-1 in the regulation of β-cell mass

The mechanism(s) by which GLP-1 modulates β-cell mass is currently a topic of intensive investigation, with a particular focus on three potential pathways: 1) enhancement of β-cell proliferation, 2) inhibition of apoptosis of β-cells, and 3) differentiation of putative stem cells in the ductal epithelium via islet neogenesis. GLP-1 exerts its actions through a prototypic seven-transmembrane-spanning, G protein-coupled receptor (GPCR) linked to activation of protein kinase A signaling (29, 30). Furthermore, considerable evidence supports coupling of the GLP-1R to multiple G proteins (31). Analyses of pancreata from rodents treated acutely or chronically with GLP-1R agonists generally demonstrates an increase in the number of proliferating β-cells (13–15, 17, 23, 32–34) (Table 1). Similarly, treatment of β-cell lines with GLP-1 increases proliferation *in vitro* (35–38). Similar studies have shown that GIP also stimulates proliferation of INS-1 cells (39). The proliferative effects of both GLP-1 and GIP involve multiple signaling pathways (Fig. 1) including phosphatidylinositol-3 kinase, Akt, MAPK and protein kinase Cζ (35–37, 39–41). The importance of specific signaling molecules as downstream mediators of the proliferative effects of GLP-1 has also been demonstrated using selective expression of dominant-negative cDNAs. Increased expression of a kinase-dead protein kinase Cζ as a functional dominant-negative protein suppressed GLP-1-induced proliferation in INS(832/13) cells (36). Similarly, overexpression of kinase-dead Akt1 completely abrogated GLP-1-induced proliferation in INS-1 cells (42). Consistent with these findings, exendin-4-treated db/db mice exhibited increased levels of pancreatic Akt and enhanced immunostaining for activated-Akt in β-cells (20).

More recent studies have implicated the src kinase, the EGFR [epidermal growth factor (EGF) receptor], and insulin

TABLE 1. Islet and β-cell growth promoting actions of GLP-1R agonists

Experimental model	GLP-1R agonist
Normal mice	GLP-1 (32)
db/db Mice	Exendin-4 (20), liraglutide (13), CJC-1131 (14)
Partially pancreatectomized rats	Exendin-4 (17, 23)
Zucker diabetic fatty rats	GLP-1 (34), liraglutide (16)
Goto-Kakizaki rat	GLP-1/exendin-4 (19)
Aging Wistar rats	GLP-1 (15)
Streptozotocin-treated newborn rats	GLP-1/exendin-4 (18)
Intrauterine growth retardation in rats	Exendin-4 (21)

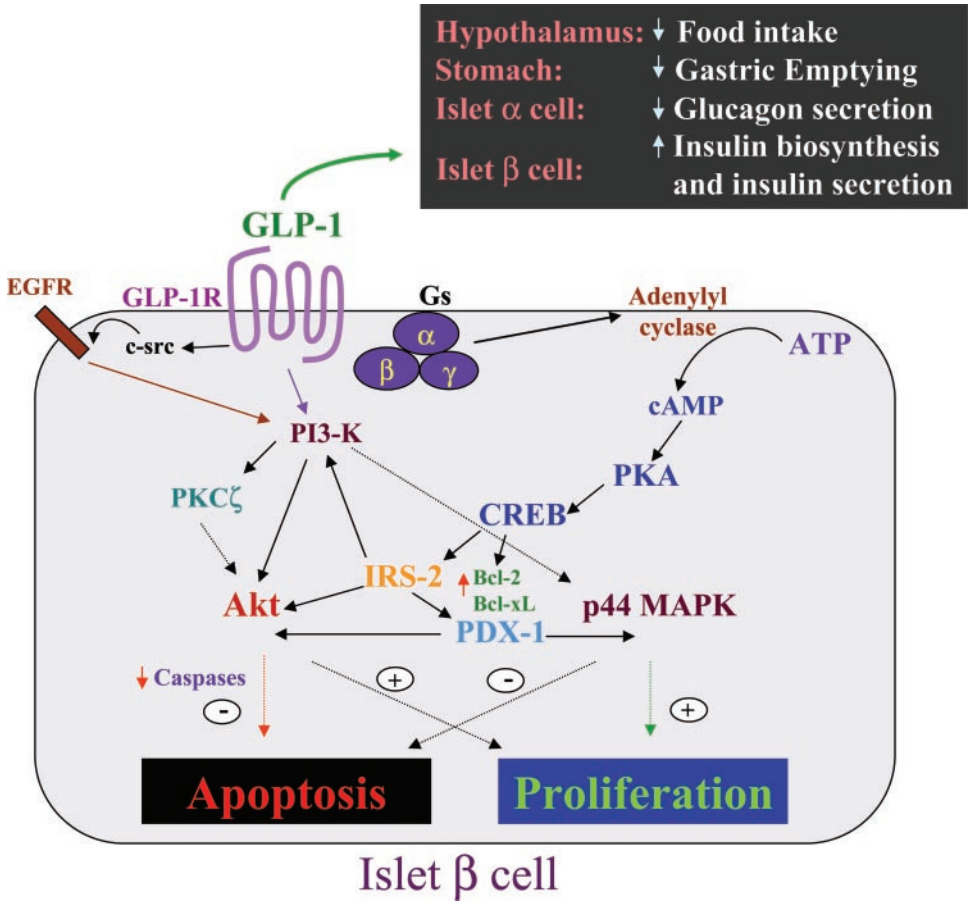

FIG. 1. GLP-1 promotes expansion of β-cell mass via indirect control of blood glucose and via direct regulation of β-cell proliferation and apoptosis. The signal transduction pathways and intermediary signaling molecules depicted in this schematic representation represent an integrated model for GLP-1 action compiled from studies of rodent and human islet cells, and immortalized islet cell lines. CREB, cAMP response element binding protein; IRS, insulin receptor substrate; PDX, pancreas duodenum homeobox; PI3-K, phosphatidylinositol 3-kinase; PKA, protein kinase A; PKC, protein kinase C.

receptor substrate-2 as additional determinants of GLP-1 action in the β-cell. Activation of GLP-1R signaling increased cell proliferation in INS(832/13) cells, whereas the src inhibitor PP1 and the EGFR-specific inhibitor AG1478 blocked GLP-1-induced cell proliferation in these cells, as well as in isolated rat islets (37). Consistent with these findings, GLP-1 stimulated EGFR phosphorylation, whereas overexpression of a dominant-negative EGFR significantly diminished GLP-1-induced β-cell proliferation in INS(832/13) cells. Furthermore, both the metalloproteinase inhibitor GM6001 and a neutralizing antibody against the EGFR ligand, betacellulin, suppressed the proliferative effect of GLP-1 (37). Taken together, these findings, together with parallel findings that the src family kinase inhibitor (PP1) and the EGFR inhibitor (AG1478) prevent inhibition of voltage-dependent K+ (Kv) channels by exendin-4 (43), imply an emerging role for src- and EGFR-dependent pathways in transduction of downstream signals activated by the GLP-1R.

More recent studies have demonstrated that GLP-1 administration also inhibits β-cell apoptosis in both rats and mice (Table 2) (20, 34, 44). Both GLP-1 and GIP increase cell survival in immortalized rodent β-cell lines when challenged with various apoptotic stimulators, including cytokines, peroxide, fatty acids, and streptozotocin (40, 41, 44–46). Importantly, the antiapoptotic actions of GLP-1 have also been demonstrated in freshly isolated human islets (47). Although the signaling pathways mediating the antiapoptotic actions of GLP-1 have not been fully elucidated (Fig. 1), evidence

TABLE 2. Antiapoptotic actions of GLP-1R agonists

Experimental model	GLP-1R agonist
db/db Mice	Exendin-4 (20)
Normal and GLP-1R−/− mice (streptozotocin)	Exendin-4 (44)
Zucker diabetic fatty rats	GLP-1 (34)
Human islet cells	GLP-1 (47)
Rat islet cells (cytokines)	Exendin-4 (44)
RINm5F islet cells (palmitate)	GLP-1/exendin-4 (46)
Min6 islet cells (hydrogen peroxide)	GLP-1 (41)
INS-1 islet cells (staurosporine)	Exendin-4 (42)

supports a role for phosphatidylinositol 3-kinase, Akt and MAPK, likely through modulation of both proapoptotic [*e.g.* caspase-3, poly(ADP-ribose) polymerase] and antiapoptotic (*e.g.* Bcl-2, Bcl-xL) proteins (40, 41, 44, 45, 47). Consistent with data from cell lines, administration of either GLP-1 or a degradation-resistant GLP-1R agonist to rodents decreases β-cell apoptosis and reduces activation of caspase-3 in the pancreas (20, 34). Furthermore, reduction of Akt activity *in vitro* prevents the antiapoptotic effect of GLP-1 (42). More recent evidence implicates a role for the transcription factor cAMP response element binding protein as a downstream mediator of the antiapoptotic actions of GLP-1, through a pathway involving cAMP response element binding protein-mediated induction of Akt via the insulin signaling protein, insulin receptor substrate-2 (48). These findings suggest a novel mechanism through which activation of protein kinase

A signaling by GLP-1 may be linked to the Akt cell survival pathway.

Studies in rodents have suggested that GLP-1 also stimulates islet neogenesis, with increased numbers of small islets noted following chronic administration of GLP-1R agonists (15, 17–20). Furthermore, GLP-1 induces the expression of pdx-1 in small ducts, a common site for islet neogenic precursors (12). Similarly, treatment of pluripotential pancreatic AR42J cells, fetal pig islet-like clusters, or undifferentiated human pancreatic progenitor or ductal cells with GLP-1R agonists induces differentiation toward a β-cell- or islet-like phenotype (49–54). The precise mechanisms linking GLP-1R activation to islet neogenesis remain to be elucidated; however, GLP-1 consistently induces the homeobox protein, pdx-1 in both β-cells and in undifferentiated precursor cells (15, 33, 35, 51, 54, 55). As pdx-1 is essential for the embryonic development of the endocrine pancreas and preservation of β-cell mass, these findings strongly implicate pdx-1 as a genetic component important for the effects of GLP-1 on islet neogenesis.

The cytotrophic and antiapoptotic actions of GLP-1 have also been demonstrated in neuronal cell lineages. GLP-1 is synthesized in selected neurons in the brain stem and hypothalamus, and the GLP-1R is widely expressed in the central nervous system. GLP-1 treatment facilitates differentiation and induces neurite outgrowth in PC12 cells, and protects rat hippocampal neurons from apoptosis (56–58). Furthermore, mice deficient in GLP-1R signaling demonstrate learning deficits and manifest enhanced neural injury after kainite administration, whereas GLP-1R agonist administration to normal animals prevents kainite-induced apoptosis (59). These findings have led to the suggestion that GLP-1 may potentially be useful for the treatment of Alzheimer's and other neurodegenerative diseases (60). In contrast, a single study has suggested that antagonism of GLP-1 action may actually enhance β amyloid-induced apoptosis in the rat (61). Further studies aimed at elucidating the role and mechanisms of action of GLP-1 in specific regions of the central nervous system are clearly warranted.

GLP-2

GLP-2, a 33-amino acid peptide, is cosecreted together with GLP-1 from gut endocrine cells in response to nutrient ingestion. Like GLP-1, GLP-2 contains an alanine at position 2 and is therefore also a substrate for N-terminal inactivation by DPP-IV (62). However, relative to GLP-1, GLP-2 exhibits a slightly longer circulating $t_{1/2}$ of several minutes *in vivo*. The initial biological action described for GLP-2 was the stimulation of adenylate cyclase activity in hypothalamic and pituitary membranes (63). Subsequent experiments demonstrated that GLP-2 was a potent growth factor for the small bowel epithelium in both mice and rats (62, 64–66). GLP-2 expands the villous epithelium predominantly through stimulation of crypt cell proliferation. Although the small bowel appears to be highly sensitive to the trophic effects of exogenous GLP-2, the colonic epithelium also exhibits a modest trophic response following GLP-2 administration (67).

The proliferative and regenerative actions of GLP-2 are most evident following the induction of experimental bowel injury. GLP-2 administration significantly improves morbidity and enhances epithelial repair in a diverse number of injury models, including enteritis and mucositis (68–78) as summarized in Table 3. The protective effect of GLP-2 on the gut may be related in part to its actions that enhance epithelial barrier function and reduce gut permeability (68, 69, 79, 80).

Although GLP-2 also reduces enterocyte and crypt apoptosis in the uninjured gastrointestinal epithelium (66, 81), the antiapoptotic actions of GLP-2 are more readily evident in the setting of epithelial injury (Table 3). Administration of nonsteroidal anti-inflammatory agents or chemotherapy activates mucosal apoptosis, whereas concomitant GLP-2 administration significantly reduces crypt apoptosis in the gut epithelium (69, 70). Interestingly, the beneficial effects of GLP-2 in a murine model of colitis were shown to be further enhanced by concomitant administration of sulfasalazine, a drug that is commonly used to reduce inflammation in patients with ulcerative colitis (78).

Elucidation of the molecular and cellular biology of the GLP-2 receptor (GLP-2R) has provided considerable insight into the diverse mechanisms activated following GLP-2 administration. The GLP-2R exhibits considerable amino acid identity with other members of the glucagon-secretin GPCR super family, including the GLP-1R (82, 83), and has been localized to rodent enteric neurons and human enteroendocrine cells (84, 85). These findings imply an indirect model for GLP-2 action whereby GLP-2R activation liberates downstream mediators which act on as yet unidentified pathways to promote crypt cell proliferation and inhibition of apoptosis (86). A number of GLP-2-regulated genes have been identified (87, 88); however, the principal downstream targets for GLP-2 action in the gut remain unknown. Although GLP-2 activates immediate early gene expression and reduces apoptosis in heterologous cells expressing a transfected GLP-2 receptor (89–91), whether the endogenous intestinal GLP-2R is coupled to identical signal transduction pathways remains to be determined. Similarly, GLP-2 and GLP-2R are found in the brain (92) and GLP-2 stimulates the proliferation of rat astrocytes *in vitro* (93), and reduces the extent of glutamate-

TABLE 3. Regenerative and cytoprotective actions of GLP-2 in the gastrointestinal tract

Intestinal injury	Model	Species
Short bowel syndrome	Massive small bowel resection	Rats (71, 72)
Small bowel enteritis	NSAIDs, genetic	Mice, rats (69, 73)
Intestinal mucositis	Chemotherapy	Mice, rats (70, 74)
Allergic enteritis	Immune sensitivity	Mice (68)
Ischemic enteritis	Superior mesenteric artery occlusion	Rats (75, 76)
Colitis	Dextran sulfate	Mice (77, 78)

NSAIDs, Nonsteroidal anti-inflammatory drugs.

induced cytotoxicity in cultured murine hippocampal cells (Lovshin, J., and D. Drucker, unpublished data). However, little is known about how GLP-2 exerts proliferative or antiapoptotic actions in the brain.

Other Gut Hormones

In addition to GLP-1, GIP, and GLP-2, a considerable number of other gut peptides exert similar trophic and antiapoptotic actions in the pancreas, small and large bowel, as reviewed in Refs. 86 and 94. Gastrin, produced in antral G cells, circulates in multiple molecular forms that exert proliferative actions in the gut. Gastrin-deficient mice exhibit reduced parietal cell mass and decreased colonocyte proliferation (95), yet have normal islet mass (96), whereas overexpression of amidated gastrin, glycine-extended gastrin, or of progastrin produces increased proliferation in the oxyntic mucosa or colon, respectively (97). Furthermore, both gastrin and progastrin exert antiapoptotic effects on cell lines *in vitro* (98, 99). Although gastrin modulates the growth of pancreatic cell lines, it does not appear to be trophic for the normal exocrine or endocrine pancreas. However, transgenic coexpression of gastrin and EGFR agonists (100), or infusion of gastrin following pancreatic transdifferentiation (101) is associated with activation of β-cell neogenesis and increased β-cell mass. Furthermore, coadministration of gastrin and EGF significantly ameliorates diabetes and induces islet regeneration in alloxan-treated mice (102). In contrast, although exogenous cholecystokinin (CCK) is trophic to the exocrine pancreas *in vivo*, disruption of CCK receptor signaling does not impair pancreatic growth in mice (103), and CCK does not appear to be an important modulator of epithelial growth in the small or large intestine. Finally, neurotensin, a tridecapeptide produced in enteroendocrine N cells predominantly in the small bowel, exerts trophic effects on the stomach, small and large intestine, and pancreas (104, 105). Although targeted inactivation of the neurotensin-1 receptor gene produces abnormalities in food intake and gut motility, whether neurotensin is essential for normal growth in the pancreas or gut has yet to be determined. Similarly, although peptide YY exerts a trophic effect on the small and large bowel mucosa (106), the physiological importance of peptide YY for gut growth remains uncertain. Hence, activation of pathways leading to cell proliferation and/or cell survival represent increasingly common actions ascribed to gut peptides (86, 94).

Gut Peptides, Growth and Apoptosis—Unanswered Questions

Accumulating evidence suggests that an increasing number of GPCRs activate signal transduction pathways coupled to cell proliferation or cell survival (86, 94, 107). Alternatively, GPCRs coupled to inhibition of cell growth, as exemplified by the somatostatin receptor family, may provide important therapeutic targets for the treatment of neoplastic disease. As many receptors for gut peptides are also expressed in neoplastic cells, there is considerable interest in examining whether antagonists of gastrin, gastrin-releasing peptide, ghrelin, neurotensin, or related peptides will attenuate the growth of human cancer cells. Furthermore, the proliferative and antiapoptotic actions of GLP-1, GLP-2 and gastrin observed in selected preclinical disease models will merit ongoing scrutiny if one or more of these agents will be used chronically in human subjects. More recent data suggesting that GLP-1R agonists activate antiapoptotic (47) and differentiation pathways (53) in human islet cells may have direct clinical relevance for efforts to preserve or expand the number of human islet β-cells. Equally intriguing are reports that GLP-1 (1–37) activates a pancreatic endocrine differentiation pathway in cultured intestinal epithelial cells (108). The therapeutic potential of regenerative medicine has sparked intense interest in understanding the molecular mechanisms controlling cell growth and cytoprotection. Accordingly, a detailed delineation of the signaling pathways activated by gut peptide GPCRs, as exemplified by GLP-1 and GLP-2, may provide new therapeutic targets for the treatment of human disorders such as diabetes and intestinal disease, respectively.

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