0013-7227/04/$15.00/0
Printed in U.S.A.

Endocrinology 145(6):2653–2659

doi: 10.1210/en.2004-0015

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

P. L. BRUBAKER AND D. J. DRUCKER

Departments of Physiology (P.L.B.) and Medicine (P.L.B., D.J.D.), the Toronto General Hospital, and the Banting and Best Diabetes Centre (D.J.D.), University of Toronto, Toronto, Ontario, Canada M5S 1A8

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, $GLP\text{-}1^{7-36NH2}$, 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.

***Endocrinology* is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**

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)

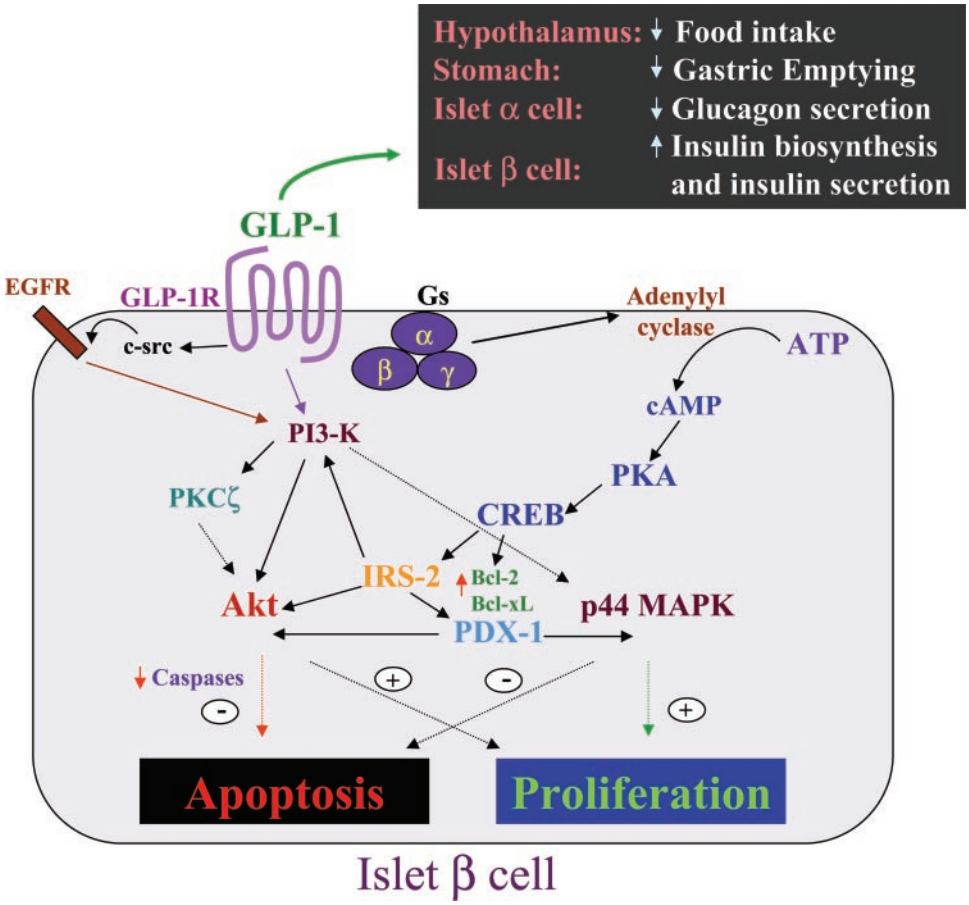

FIG. 1. GLP-1 promotes expansion of β-cell mass via indirect control of blood glucose and via direct regulation of β-cell proliferation and apoptosis. The signal transduction pathways and intermediary signaling molecules depicted in this schematic representation represent an integrated model for GLP-1 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.

Acknowledgments

Received January 7, 2004. Accepted January 30, 2004.

Address all correspondence and requests for reprints to: Dr. P. L. Brubaker, Room 3366, Medical Science Building, University of Toronto, 1 King's College Circle, Toronto, Ontario, Canada M5S 1A8. E-mail: p.brubaker@utoronto.ca.

This work was supported in part by grants from the Canadian Institutes of Health Research (to P.L.B. and D.J.D.), Canadian Diabetes Association (to P.L.B. and D.J.D.), Crohn's and Colitis Foundation of Canada (to P.L.B.), Juvenile Diabetes Research Foundation (to D.J.D.), National Cancer Institute of Canada (to D.J.D.) and the Ontario Research and Development Challenge Fund (to D.J.D.). P.L.B. is a Canada Research Chair in Vascular and Metabolic Biology, and D.J.D. is a Senior Scientist of the Canadian Institutes of Health Research.

References

1. **Creutzfeldt W** 1979 The incretin concept today. Diabetologia 16:75–85
2. **Drucker DJ** 2003 Enhancing incretin action for the treatment of type 2 diabetes. Diabetes Care 26:2929–2940
3. **Scrocchi LA, Brown TJ, MacLusky N, Brubaker PL, Auerbach AB, Joyner AL, Drucker DJ** 1996 Glucose intolerance but normal satiety in mice with a null mutation in the glucagon-like peptide receptor gene. Nature Med 2:1254–1258
4. **Miyawaki K, Yamada Y, Yano H, Niwa H, Ban N, Ihara Y, Kubota A, Fujimoto S, Kajikawa M, Kuroe A, Tsuda K, Hashimoto H, Yamashita T, Jomori T, Tashiro F, Miyazaki J, Seino Y** 1999 Glucose intolerance caused by a defect in the entero-insular axis: a study in gastric inhibitory polypeptide receptor knockout mice. Proc Natl Acad Sci USA 96:14843–14847
5. **Drucker DJ** 2003 Therapeutic potential of dipeptidyl peptidase IV inhibitors for the treatment of type 2 diabetes. Expert Opin Investig Drugs 12:87–100
6. **Nauck MA, Heimesaat MM, Orskov C, Holst JJ, Ebert R, Creutzfeldt W** 1993 Preserved incretin activity of glucagon-like peptide 1 [7–36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. J Clin Invest 91:301–307
7. **Zander M, Madsbad S, Madsen JL, Holst JJ** 2002 Effect of 6-week course of glucagon-like peptide 1 on glycaemic control, insulin sensitivity, and β-cell function in type 2 diabetes: a parallel-group study. Lancet 359:824–830
8. **Ahren B, Simonsson E, Larsson H, Landin-Olsson M, Torgeirsson H, Jansson PA, Sandqvist M, Bavenholm P, Efendic S, Eriksson JW, Dickinson S, Holmes D** 2002 Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4-week study period in type 2 diabetes. Diabetes Care 25:869–875
9. **Fineman MS, Bicsak TA, Shen LZ, Taylor K, Gaines E, Varns A, Kim DW, Baron AD** 2003 Effect on glycemic control of synthetic exendin-4 (AC2993) additive to existing metformin and/or sulfonylurea treatment in patients with type 2 diabetes. Diabetes Care 27:2370–2377
10. **Yoon KH, Ko SH, Cho JH, Lee JM, Ahn YB, Song KH, Yoo SJ, Kang MI, Cha BY, Lee KW, Son HY, Kang SK, Kim HS, Lee IK, Bonner-Weir S** 2003 Selective β-cell loss and α-cell expansion in patients with type 2 diabetes mellitus in Korea. J Clin Endocrinol Metab 88:2300–2308
11. **Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC** 2003

β-Cell deficit and increased β-cell apoptosis in humans with type 2 diabetes. Diabetes 52:102–110
12. **Stoffers DA, Kieffer TJ, Hussain MA, Drucker DJ, Egan JM, Bonner-Weir S, Habener JF** 2000 Insulinotropic glucagon-like peptide-1 agonists stimulate expression of homeodomain protein IDX-1 and increase β-cell mass in mouse pancreas. Diabetes 49:741–748
13. **Rolin B, Larsen MO, Gotfredsen CF, Deacon CF, Carr RD, Wilken M, Knudsen LB** 2002 The long-acting GLP-1 derivative NN2211 ameliorates glycemia and increases β-cell mass in diabetic mice. Am J Physiol Endocrinol Metab 283:E745–E752
14. **Kim JG, Baggio LL, Bridon DP, Castaigne JP, Robitaille MF, Jette L, Benquet C, Drucker DJ** 2003 Development and characterization of a glucagon-like peptide 1-albumin conjugate: the ability to activate the glucagon-like peptide 1 receptor in vivo. Diabetes 52:751–759
15. **Perfetti R, Zhou J, Doyle ME, Egan JM** 2000 Glucagon-like peptide-1 induces cell proliferation and pancreatic-duodenum homeobox-1 expression and increases endocrine cell mass in the pancreas of old, glucose-intolerant rats. Endocrinology 141:4600–4605
16. **Sturis J, Gotfredsen CF, Romer J, Rolin B, Ribel U, Brand CL, Wilken M, Wassermann K, Deacon CF, Carr RD, Knudsen LB** 2003 GLP-1 derivative liraglutide in rats with β-cell deficiencies: influence of metabolic state on β-cell mass dynamics. Br J Pharmacol 140:123–132
17. **Xu G, Stoffers DA, Habener JF, Bonner-Weir S** 1999 Exendin-4 stimulates both β-cell replication and neogenesis, resulting in increased β-cell mass and improved glucose tolerance in diabetic rats. Diabetes 48:2270–2276
18. **Tourrel C, Bailbe D, Meile M-J, Kergoat M, Portha B** 2001 Glucagon-like peptide-1 and exendin-4 stimulate β-cell neogenesis in streptozotocin-treated newborn rats resulting in persistently improved glucose homeostasis at adult age. Diabetes 50:1562–1570
19. **Tourrel C, Bailbe D, Lacorne M, Meile MJ, Kergoat M, Portha B** 2002 Persistent improvement of type 2 diabetes in the Goto-Kakizaki rat model by expansion of the β-cell mass during the prediabetic period with glucagon-like peptide-1 or exendin-4. Diabetes 51:1443–1452
20. **Wang Q, Brubaker PL** 2002 Glucagon-like peptide-1 treatment delays the onset of diabetes in 8 week-old db/db mice. Diabetologia 45:1263–1273
21. **Stoffers DA, Desai BM, DeLeon DD, Simmons RA** 2003 Neonatal exendin-4 prevents the development of diabetes in the intrauterine growth retarded rat. Diabetes 52:734–740
22. **Baggio L, Adatia F, Bock T, Brubaker PL, Drucker DJ** 2000 Sustained expression of exendin-4 does not perturb glucose homeostasis, β cell mass or food intake in metallothionein-preproexendin transgenic mice. J Biol Chem 275:34471–34477
23. **De Leon DD, Deng S, Madani R, Ahima RS, Drucker DJ, Stoffers DA** 2003 Role of endogenous glucagon-like peptide-1 in islet regeneration following partial pancreatectomy. Diabetes 52:365–371
24. **Pospisilik JA, Martin J, Doty T, Ehses JA, Pamir N, Lynn FC, Piteau S, Demuth HU, McIntosh CH, Pederson RA** 2003 Dipeptidyl peptidase IV inhibitor treatment stimulates β-cell survival and islet neogenesis in streptozotocin-induced diabetic rats. Diabetes 52:741–750
25. **Conarello SL, Li Z, Ronan J, Roy RS, Zhu L, Jiang G, Liu F, Woods J, Zycband E, Moller DE, Thornberry NA, Zhang BB** 2003 Mice lacking dipeptidyl peptidase IV are protected against obesity and insulin resistance. Proc Natl Acad Sci USA 100:6825–6830
26. **Pamir N, Lynn FC, Buchan AM, Ehses J, Hinke SA, Pospisilik JA, Miyawaki K, Yamada Y, Seino Y, McIntosh CH, Pederson RA** 2003 Glucose-dependent insulinotropic polypeptide receptor null mice exhibit compensatory changes in the enteroinsular axis. Am J Physiol Endocrinol Metab 284:E931–E939
27. **Ling Z, Wu D, Zambre Y, Flamez D, Drucker DJ, Pipeleers DG, Schuit FC** 2001 Glucagon-like peptide 1 receptor signaling influences topography of islet cells in mice. Virchows Arch 438:382–387
28. **Scrocchi LA, Hill ME, Saleh J, Perkins B, Drucker DJ** 2000 Elimination of GLP-1R signaling does not modify weight gain and islet adaptation in mice with combined disruption of leptin and GLP-1 action. Diabetes 49:1552–1560
29. **Thorens B** 1992 Expression cloning of the pancreatic β cell receptor for the gluco-incretin hormone glucagon-like peptide 1. Proc Natl Acad Sci USA 89:8641–8645
30. **Brubaker PL, Drucker DJ** 2002 Structure-function of the glucagon receptor family of G protein-coupled receptors: the glucagon, GIP, GLP-1, and GLP-2 receptors. Receptors Channels 8:179–188
31. **Montrose-Rafizadeh C, Avdonin P, Garant MJ, Rodgers BD, Kole S, Yang H, Levine MA, Schwindinger W, Bernier M** 1999 Pancreatic glucagon-like peptide-1 receptor couples to multiple G proteins and activates mitogen-activated protein kinase pathways in Chinese hamster ovary cells. Endocrinology 140:1132–1140
32. **Edvell A, Lindstrom P** 1999 Initiation of increased pancreatic islet growth in young normoglycemic mice (Umea +/?). Endocrinology 140:778–783
33. **Wang X, Cahill CM, Pineyro MA, Zhou J, Doyle ME, Egan JM** 1999 Glucagon-like peptide-1 regulates the β cell transcription factor, PDX-1, in insulinoma cells. Endocrinology 140:4904–4907
34. **Farilla L, Hui H, Bertolotto C, Kang E, Bulotta A, Di Mario U, Perfetti R** 2002 Glucagon-like peptide-1 promotes islet cell growth and inhibits apoptosis in zucker diabetic rats. Endocrinology 143:4397–4408
35. **Buteau J, Roduit R, Susini S, Prentki M** 1999 Glucagon-like peptide-1 promotes DNA synthesis, activates phosphatidylinositol 3-kinase and increases transcription factor pancreatic and duodenal homeobox gene 1 (PDX-1) DNA binding activity in β (INS-1)-cells. Diabetologia 42:856–864
36. **Buteau J, Foisy S, Rhodes CJ, Carpenter L, Biden TJ, Prentki M** 2001 Protein kinase Cζ activation mediates glucagon-like peptide-1-induced pancreatic β-cell proliferation. Diabetes 50:2237–2243
37. **Buteau J, Foisy S, Joly E, Prentki M** 2003 Glucagon-like peptide 1 induces pancreatic β-cell proliferation via transactivation of the epidermal growth factor receptor. Diabetes 52:124–132
38. **Stark A, Mentlein R** 2002 Somatostatin inhibits glucagon-like peptide-1-induced insulin secretion and proliferation of RINm5F insulinoma cells. Regul Pept 108:97–102
39. **Trumper A, Trumper K, Trusheim H, Arnold R, Goke B, Horsch D** 2001 Glucose-dependent insulinotropic polypeptide is a growth factor for β (INS-1) cells by pleiotropic signaling. Mol Endocrinol 15:1559–1570
40. **Trumper A, Trumper K, Horsch D** 2002 Mechanisms of mitogenic and anti-apoptotic signaling by glucose-dependent insulinotropic polypeptide in β(INS-1)-cells. J Endocrinol 174:233–246
41. **Hui H, Nourparvar A, Zhao X, Perfetti R** 2003 Glucagon-like peptide-1 inhibits apoptosis of insulin-secreting cells via a cyclic 5′-adenosine monophosphate-dependent protein kinase A- and a phosphatidylinositol 3-kinase-dependent pathway. Endocrinology 144:1444–1455
42. **Wang Q, Li L, Xu E, Wong V, Rhodes CJ, Brubaker PL** 5 Feb 2004 Glucagon-like peptide-1 regulates proliferation and apoptosis via activation of protein kinase B in pancreatic (INS-1) β-cells. Diabetologia 14762654
43. **MacDonald PE, Wang X, Xia F, El-kholy W, Targonsky ED, Tsushima RG, Wheeler MB** 2003 Antagonism of rat β-cell voltage-dependent K+ currents by exendin 4 requires dual activation of the cAMP/protein kinase A and phosphatidylinositol 3-kinase signaling pathways. J Biol Chem 278:52446–52453
44. **Li Y, Hansotia T, Yusta B, Ris F, Halban PA, Drucker DJ** 2003 Glucagon-like peptide-1 receptor signaling modulates β cell apoptosis. J Biol Chem 278:471–478
45. **Ehses JA, Casilla VR, Doty T, Pospisilik JA, Winter KD, Demuth HU, Pederson RA, McIntosh CH** 2003 Glucose-dependent insulinotropic polypeptide promotes β-(INS-1) cell survival via cyclic adenosine monophosphate-mediated caspase-3 inhibition and regulation of p38 mitogen-activated protein kinase. Endocrinology 144:4433–4445
46. **Kwon G, Pappan KL, Marshall CA, Schaffer JE, McDaniel ML** 2004 Cyclic AMP dose-dependently prevents palmitate-induced apoptosis by both PKA- and cAMP-GEF-dependent pathways in β-cells. J Biol Chem 279:8938–8945
47. **Farilla L, Bulotta A, Hirshbirg B, Li Calzi S, Khoury N, Noushmehr H, Bertolotto C, Di Mario U, Harlan DM, Perfetti R** 2003 GLP-1 inhibits cell apoptosis and improves glucose responsiveness of freshly isolated human islets. Endocrinology 144:5149–5158
48. **Jhala US, Canettieri G, Screaton RA, Kulkarni RN, Krajewski S, Reed J, Walker J, Lin X, White M, Montminy M** 2003 cAMP promotes pancreatic β-cell survival via CREB-mediated induction of IRS2. Genes Dev 17:1575–1580
49. **Zhou J, Wang X, Pineyro MA, Egan JM** 1999 Glucagon-like peptide 1 and exendin-4 convert pancreatic AR42J cells into glucagon- and insulin-producing cells. Diabetes 48:2358–2366
50. **Movassat J, Beattie GM, Lopez AD, Hayek A** 2002 Exendin 4 up-regulates expression of PDX 1 and hastens differentiation and maturation of human fetal pancreatic cells. J Clin Endocrinol Metab 87:4775–4781
51. **Hardikar AA, Wang XY, Williams LJ, Kwok J, Wong R, Yao M, Tuch BE** 2002 Functional maturation of fetal porcine β-cells by glucagon-like peptide 1 and cholecystokinin. Endocrinology 143:3505–3514
52. **Bulotta A, Hui H, Anastasi E, Bertolotto C, Boros LG, Di Mario U, Perfetti R** 2002 Cultured pancreatic ductal cells undergo cell cycle re-distribution and β-cell-like differentiation in response to glucagon-like peptide-1. J Mol Endocrinol 29:347–360
53. **Abraham EJ, Leech CA, Lin JC, Zulewski H, Habener JF** 2002 Insulinotropic hormone glucagon-like peptide-1 differentiation of human pancreatic islet-derived progenitor cells into insulin-producing cells. Endocrinology 143:3152–3161
54. **Zhou J, Pineyro MA, Wang X, Doyle ME, Egan JM** 2002 Exendin-4 differentiation of a human pancreatic duct cell line into endocrine cells: involvement of PDX-1 and HNF3β transcription factors. J Cell Physiol 192:304–314
55. **Wang X, Zhou J, Doyle ME, Egan JM** 2001 Glucagon-like peptide-1 causes pancreatic duodenal homeobox-1 protein translocation from the cytoplasm to the nucleus of pancreatic β-cells by a cyclic adenosine monophosphate/protein kinase A-dependent mechanism. Endocrinology 142:1820–1827
56. **Perry T, Lahiri DK, Chen D, Zhou J, Shaw KT, Egan JM, Greig NH** 2002 A novel neurotrophic property of glucagon-like peptide 1: a promoter of nerve growth factor-mediated differentiation in PC12 cells. J Pharmacol Exp Ther 300:958–966
57. **Perry T, Haughey NJ, Mattson MP, Egan JM, Greig NH** 2002 Protection and reversal of excitotoxic neuronal damage by glucagon-like peptide-1 and exendin-4. J Pharmacol Exp Ther 302:881–888
58. **Perry T, Lahiri DK, Sambamurti K, Chen D, Mattson MP, Egan JM, Greig NH** 2003 Glucagon-like peptide-1 decreases endogenous amyloid-β peptide

(Aβ) levels and protects hippocampal neurons from death induced by Aβ and iron. J Neurosci Res 72:603–612
59. **During MJ, Cao L, Zuzga DS, Francis JS, Fitzsimons HL, Jiao X, Bland RJ, Klugmann M, Banks WA, Drucker DJ, Haile CN** 2003 Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. Nat Med 9:1173–1179
60. **Perry T, Greig NH** 2002 The glucagon-like peptides: a new genre in therapeutic targets for intervention in Alzheimer's disease. J Alzheimers Dis 4:487–496
61. **Oka J, Suzuki E, Kondo Y** 2000 Endogenous GLP-1 is involved in β-amyloid protein-induced memory impairment and hippocampal neuronal death in rats. Brain Res 878:194–198
62. **Drucker DJ, Shi Q, Crivici A, Sumner-Smith M, Tavares W, Hill M, DeForest L, Cooper S, Brubaker PL** 1997 Regulation of the biological activity of glucagon-like peptide 2 in vivo by dipeptidyl peptidase IV. Nat Biotechnol 15:673–677
63. **Hoosein NM, Gurd RS** 1984 Human glucagon-like peptides 1 and 2 activate rat brain adenylate cyclase. FEBS Lett 178:83–86
64. **Drucker DJ, Ehrlich P, Asa SL, Brubaker PL** 1996 Induction of intestinal epithelial proliferation by glucagon-like peptide 2. Proc Natl Acad Sci USA 93:7911–7916
65. **Tsai C-H, Hill M, Drucker DJ** 1997 Biological determinants of intestinotrophic properties of GLP-2 in vivo. Am J Physiol 272:G662–G668
66. **Tsai C-H, Hill M, Asa SL, Brubaker PL, Drucker DJ** 1997 Intestinal growth-promoting properties of glucagon-like peptide 2 in mice. Am J Physiol 273: E77–E84
67. **Drucker DJ, DeForest L, Brubaker PL** 1997 Intestinal response to growth factors administered alone or in combination with human [Gly2]glucagon-like peptide 2. Am J Physiol 273:G1252–G1262
68. **Cameron HL, Yang PC, Perdue MH** 2003 Glucagon-like peptide-2-enhanced barrier function reduces pathophysiology in a model of food allergy. Am J Physiol Gastrointest Liver Physiol 284:G905–G912
69. **Boushey RP, Yusta B, Drucker DJ** 1999 Glucagon-like peptide 2 decreases mortality and reduces the severity of indomethacin-induced murine enteritis. Am J Physiol 277:E937–E947
70. **Boushey RP, Yusta B, Drucker DJ** 2001 Glucagon-like peptide (GLP)-2 reduces chemotherapy-associated mortality and enhances cell survival in cells expressing a transfected GLP-2 receptor. Cancer Res 61:687–693
71. **Scott RB, Kirk D, MacNaughton WK, Meddings JB** 1998 GLP-2 augments the adaptive response to massive intestinal resection in rat. Am J Physiol 275:G911–G921
72. **Sigalet DL, Martin GR** 2000 Hormonal therapy for short bowel syndrome. J Pediatr Surg 35:360–364
73. **Alavi K, Schwartz MZ, Palazzo JP, Prasad R** 2000 Treatment of inflammatory bowel disease in a rodent model with the intestinal growth factor glucagon-like peptide-2. J Pediatr Surg 35:847–851
74. **Tavakkolizadeh A, Shen R, Abraham P, Kormi N, Seifert P, Edelman ER, Jacobs DO, Zinner MJ, Ashley SW, Whang EE** 2000 Glucagon-like peptide 2: a new treatment for chemotherapy-induced enteritis. J Surg Res 91:77–82
75. **Prasad R, Alavi K, Schwartz MZ** 2000 Glucagonlike peptide-2 analogue enhances intestinal mucosal mass after ischemia and reperfusion. J Pediatr Surg 35:357–359
76. **Prasad R, Alavi K, Schwartz MZ** 2001 GLP-2α accelerates recovery of mucosal absorptive function after intestinal ischemia/reperfusion. J Pediatr Surg 36:570–572
77. **Drucker DJ, Yusta B, Boushey RP, Deforest L, Brubaker PL** 1999 Human [Gly2]-GLP-2 reduces the severity of colonic injury in a murine model of experimental colitis. Am J Physiol 276:G79–G91
78. **L'Heureux MC, Brubaker PL** 2003 Glucagon-like peptide-2 and common therapeutics in a murine model of ulcerative colitis. J Pharmacol Exp Ther 306:347–354
79. **Benjamin MA, McKay DM, Yang PC, Cameron H, Perdue MH** 2000 Glucagon-like peptide-2 enhances intestinal epithelial barrier function of both transcellular and paracellular pathways in the mouse. Gut 47:112–119
80. **Kouris GJ, Liu Q, Rossi H, Djuricin G, Gattuso P, Nathan C, Weinstein RA, Prinz RA** 2001 The effect of glucagon-like peptide 2 on intestinal permeability and bacterial translocation in acute necrotizing pancreatitis. Am J Surg 181: 571–575
81. **Burrin DG, Stoll B, Jiang R, Petersen Y, Elnif J, Buddington RK, Schmidt M, Holst JJ, Hartmann B, Sangild PT** 2000 GLP-2 stimulates intestinal growth in premature TPN-fed pigs by suppressing proteolysis and apoptosis. Am J Physiol Gastrointest Liver Physiol 279:G1249–G1256
82. **Munroe DG, Gupta AK, Kooshesh F, Vyas TB, Rizkalla G, Wang H, Demchyshyn L, Yang ZJ, Kamboj RK, Chen H, McCallum K, Sumner-Smith M, Drucker DJ, Crivici A** 1999 Prototypic G protein-coupled receptor for the intestinotrophic factor glucagon-like peptide 2. Proc Natl Acad Sci USA 96:1569–1573
83. **Mayo KE, Miller LJ, Bataille D, Dalle S, Goke B, Thorens B, Drucker DJ** 2003 International Union of Pharmacology. XXXV. The glucagon receptor family. Pharmacol Rev 55:167–194
84. **Bjerknes M, Cheng H** 2001 Modulation of specific intestinal epithelial progenitors by enteric neurons. Proc Natl Acad Sci USA 98:12497–12502
85. **Yusta B, Huang L, Munroe D, Wolff G, Fantaske R, Sharma S, Demchyshyn L, Asa SL, Drucker DJ** 2000 Enteroendocrine localization of GLP-2 receptor expression. Gastroenterology 119:744–755
86. **Drucker DJ** 2003 Glucagon-like peptides: regulators of cell proliferation, differentiation, and apoptosis. Mol Endocrinol 17:161–171
87. **Petersen YM, Elnif J, Schmidt M, Sangild PT** 2002 Glucagon-like peptide 2 enhances maltase-glucoamylase and sucrase-isomaltase gene expression and activity in parenterally fed premature neonatal piglets. Pediatr Res 52:498–503
88. **Swietlicki E, Iordanov H, Fritsch C, Yi L, Levin MS, Rubin DC** 2003 Growth factor regulation of PC4/TIS7, an immediate early gene expressed during gut adaptation after resection. J Parenter Enteral Nutr 27:123–131
89. **Yusta B, Somwar R, Wang F, Munroe D, Grinstein S, Klip A, Drucker DJ** 1999 Identification of glucagon-like peptide-2 (GLP-2)-activated signaling pathways in baby hamster kidney fibroblasts expressing the rat GLP-2 receptor. J Biol Chem 274:30459–30467
90. **Yusta B, Estall J, Drucker DJ** 2002 Glucagon-like peptide-2 receptor activation engages Bad and glycogen synthase kinase 3 in a protein kinase A-dependent manner and prevents apoptosis following inhibition of phosphatidylinositol 3-kinase. J Biol Chem 277:24896–24906
91. **Yusta B, Boushey RP, Drucker DJ** 2000 The glucagon-like peptide-2 receptor mediates direct inhibition of cellular apoptosis via a cAMP-dependent protein kinase-independent pathway. J Biol Chem 275:35345–35352
92. **Lovshin J, Estall J, Yusta B, Brown TJ, Drucker DJ** 2001 Glucagon-like peptide-2 action in the murine central nervous system is enhanced by elimination of GLP-1 receptor signaling. J Biol Chem 276:21489–21499
93. **Velazquez E, Ruiz-Albusac JM, Blazquez E** 2003 Glucagon-like peptide-2 stimulates the proliferation of cultured rat astrocytes. Eur J Biochem 270: 3001–3009
94. **Thomas RP, Hellmich MR, Townsend Jr CM, Evers BM** 2003 Role of gastrointestinal hormones in the proliferation of normal and neoplastic tissues. Endocr Rev 24:571–599
95. **Koh TJ, Goldenring JR, Ito S, Mashimo H, Kopin AS, Varro A, Dockray GJ, Wang TC** 1997 Gastrin deficiency results in altered gastric differentiation and decreased colonic proliferation in mice. Gastroenterology 113:1015–1025
96. **Boushey RP, Abadir A, Flamez D, Baggio LL, Li Y, Berger V, Marshall BA, Finegood D, Wang TC, Schuit F, Drucker DJ** 2003 Hypoglycemia, defective islet glucagon secretion, but normal islet mass in mice with a disruption of the gastrin gene. Gastroenterology 125:1164–1174
97. **Johnson LR, Guthrie PD** 1976 Stimulation of DNA synthesis by big and little gastrin (G-34 and G-17). Gastroenterology 71:599–602
98. **Todisco A, Ramamoorthy S, Witham T, Pausawasdi N, Srinivasan S, Dickinson CJ, Askari FK, Krametter D** 2001 Molecular mechanisms for the antiapoptotic action of gastrin. Am J Physiol Gastrointest Liver Physiol 280: G298–G307
99. **Wu H, Owlia A, Singh P** 2003 Precursor peptide progastrin(1–80) reduces apoptosis of intestinal epithelial cells and upregulates cytochrome c oxidase Vb levels and synthesis of ATP. Am J Physiol Gastrointest Liver Physiol 285:G1097–G1110
100. **Wang TC, Bonner-Weir S, Oates PS, Chulak M, Simon B, Merlino GT, Schmidt EV, Brand SJ** 1993 Pancreatic gastrin stimulates islet differentiation of transforming growth factor α-induced ductular precursor cells. J Clin Invest 92:1349–1356
101. **Rooman I, Lardon J, Bouwens L** 2002 Gastrin stimulates β-cell neogenesis and increases islet mass from transdifferentiated but not from normal exocrine pancreas tissue. Diabetes 51:686–690
102. **Rooman I, Bouwens L** 2004 Combined gastrin and epidermal growth factor treatment induces islet regeneration and restores normoglycaemia in C57Bl6/J mice treated with alloxan. Diabetologia 47:259–265
103. **Kopin AS, Mathes WF, McBride EW, Nguyen M, Al-Haider W, Schmitz F, Bonner-Weir S, Kanarek R, Beinborn M** 1999 The cholecystokinin-A receptor mediates inhibition of food intake yet is not essential for the maintenance of body weight. J Clin Invest 103:383–391
104. **Feurle GE, Muller B, Ohnheiser G, Baca I** 1985 Action of neurotensin on size, composition, and growth of pancreas and stomach in the rat. Regul Pept 13:53–62
105. **Wood JG, Hoang HD, Bussjaeger LJ, Solomon TE** 1988 Neurotensin stimulates growth of small intestine in rats. Am J Physiol 255:G813–G817
106. **Gomez G, Zhang T, Rajaraman S, Thakore KN, Yanahara N, Townsend Jr CM, Thompson JC, Greeley GH** 1995 Intestinal PYY: ontogeny of gene expression in rat bowel and trophic actions on rat and mouse bowel. Am J Physiol 268:G71–G81
107. **Pierce KL, Luttrell LM, Lefkowitz RJ** 2001 New mechanisms in heptahelical receptor signaling to mitogen activated protein kinase cascades. Oncogene 20:1532–1539
108. **Suzuki A, Nakauchi H, Taniguchi H** 2003 Glucagon-like peptide 1 (1–37) converts intestinal epithelial cells into insulin-producing cells. Proc Natl Acad Sci USA 100:5034–5039

Endocrinology **is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**