

Proglucagon-Derived Peptides: Mechanisms of Action and Therapeutic Potential

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Glucagon is used for the treatment of hypoglycemia, and glucagon receptor antagonists are under development for the treatment of type 2 diabetes. Moreover, glucagon-like peptide (GLP)-1 and GLP-2 receptor agonists appear to be promising therapies for the treatment of type 2 diabetes and intestinal disorders, respectively. This review discusses the physiological, pharmacological, and therapeutic actions of the proglucagon-derived peptides, with an emphasis on clinical relevance of the peptides for the treatment of human disease.

The proglucagon-derived peptides (PGDPs) are encoded by a single mammalian proglucagon gene. Tissue-specific posttranslational processing mediated by prohormone convertase (PC) enzymes liberates these peptide hormones in a tissue-specific manner (FIGURE 1). PC1/3 is essential for generation of the glucagon-like peptides (GLPs) in enteroendocrine cells (38, 101), whereas PC2 is critical for processing of pancreatic glucagon from islet α -cells (52, 102). The PGDPs are released from endocrine cells in response to changes in blood glucose (pancreatic glucagon in the islets) or nutrient ingestion (GLP-1 and GLP-2 in the intestine) and exert their effects through distinct G protein-coupled receptors (GPCRs).

Glucagon is released from the α -cells of the pancreatic islets of Langerhans in response to reduced

levels of blood glucose, and it stimulates glucose production and glycogen breakdown in the liver. Gut-derived GLP-1 and GLP-2 regulate multiple pathways promoting glucose homeostasis and energy absorption, respectively. GLP-1 and GLP-2 also increase β -cell and intestinal mucosal mass, respectively, by increasing proliferation and inhibiting apoptosis (39). The physiological importance of the remaining PGDPs is less well-defined, and separate receptor(s) for either glicentin or oxyntomodulin have not yet been identified.

Enteroglucagon

The term enteroglucagon refers to intestinal GLPs, principally glicentin and oxyntomodulin, that exhibit overlapping immunoreactivity when incubated with various antisera directed against glucagon. Glicentin and oxyntomodulin are liberated from proglucagon in gut endocrine cells and are

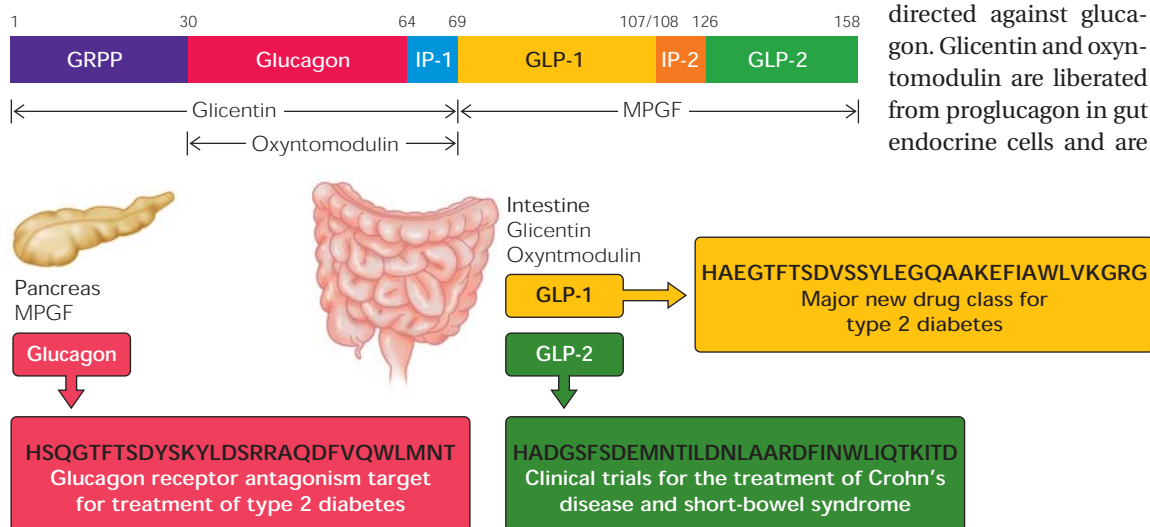


FIGURE 1. Structural organization of proglucagon and the proglucagon-derived peptides

Peptides liberated specifically in the pancreas or intestine are indicated below the full-length proglucagon sequence along with their amino acid sequence and therapeutic potential. The numerals above the proglucagon structure indicate the relative amino acid positions of the proglucagon-derived peptides within proglucagon. GLP, glucagon-like peptide; GRPP, glicentin-related pancreatic peptide; MPGF, major proglucagon-derived fragment; IP, intervening peptide.



cosecreted from intestinal L-cells together with GLP-1 and GLP-2 (93). Glicentin stimulates insulin and inhibits glucagon secretion (91), inhibits gastric acid secretion (77), regulates gut motility (111), and stimulates gut growth (40, 89). Given the pharmacological concentrations of glicentin used in these studies, together with the absence of a separate glicentin receptor, it seems likely that at least some of these actions are attributable to activation of either glucagon, GLP-1, or GLP-2 receptors.

Oxyntomodulin is a 37-amino-acid peptide that stimulates insulin secretion, slows gastric emptying, and inhibits gastric acid secretion (65, 66, 106, 107). Oxyntomodulin also stimulates intestinal glucose uptake and decreases pancreatic enzyme secretion in rats (5, 30), whereas central intracerebroventricular administration of oxyntomodulin leads to a reduction in food intake in both fed and fasted rodents (33). The mechanism whereby oxyntomodulin exerts these effects is still unclear; however, oxyntomodulin displays weak activity for the glucagon receptor (Gcgr) and may weakly mimic glucagon action in the liver and pancreas (8). Furthermore, the anorectic effect of oxyntomodulin in rats can be blocked by the GLP-1 receptor antagonist exendin-(9–39) (33). The anorectic actions of oxyntomodulin are detectable in the absence of functional glucagon receptors but are absent in GLP-1 receptor (GLP-1R) $-/-$ mice, further suggesting that oxyntomodulin regulates food intake through the GLP-1R (6). Oxyntomodulin reduces food intake and induces satiety in short-term studies of healthy human subjects (29). The long-term actions of oxyntomodulin on body weight in obese human subjects have recently been reported (123a).

Glucagon

Synthesis and secretion

Glucagon is a 29-amino-acid peptide hormone released from islet α -cells in response to hypoglycemia and is the main counterregulatory hormone to insulin (32) with the insulin-to-glucagon ratio determining the control of hepatic glucose production through rates of gluconeogenesis and glycogenolysis (FIGURE 2).

Gcgr

Gcgr contains 485 amino acids, shares 42% sequence identity with the GLP-1 receptor, and is a member of the secretin-glucagon receptor class II family of GPCRs (67, 86). Gcgr activation stimulates adenylate cyclase and increases levels of intracellular calcium. Glucagon binding sites and RNA transcripts have been identified in liver, kidney, intestinal smooth muscle, brain, and islet β -

cells and possibly in fat (45, 60, 116).

Physiology and therapeutic potential

Diabetes has long been viewed as a bihormonal disease (121) with insulin deficiency or insulin resistance, together with glucagon excess, leading to the development of hyperglycemia. Conversely, a substantial literature documents the importance of normal glucagon secretion for counterregulation during insulin-induced hypoglycemia (31, 32), and susceptible individuals with type 1 diabetes may use glucagon as an adjunctive therapy for the treatment of severe hypoglycemia. Studies in type 2 diabetics reveal that a lack of glucagon suppression contributes to increased postprandial hyperglycemia, due in part to accelerated glycogenolysis (110). Accordingly, glucagon receptor antagonists represent a potential approach for the treatment of type 2 diabetes (70), and both peptide and nonpeptide antagonists of the glucagon receptor block the hyperglycemic effect of exogenous glucagon in normal and diabetic animals (69).

Several experimental approaches have demonstrated the importance of endogenous glucagon for development of hyperglycemia in experimental models of diabetes. Neutralizing glucagon antibodies abolished the postprandial increase in glucose levels in moderately hyperglycemic streptozotocin-diabetic rats (16). More recently, antisense oligonucleotides against the Gcgr decreased levels of liver glucagon mRNA and significantly reduced blood glucose, triglycerides, and free fatty acids in *db/db* mice (82). Similar experiments employing Gcgr antisense oligonucleotides ameliorated experimental diabetes in *db/db* and *ob/ob* mice and in the Zucker diabetic fatty rat (115). Remarkably, both transient and complete genetic attenuation of Gcgr expression is associated with the development of islet α -cell hyperplasia, increased pancreatic insulin content, and raised circulating levels of plasma GLP-1 (53, 115). Hence, attenuation of glucagon receptor signaling exerts antidiabetic effects directly via modulation of hepatocyte glucose production and indirectly via increased pancreatic generation of bioactive GLP-1.

A number of nonpeptide glucagon receptor antagonists with diverse structures have been described and studied in both rodent and human models. The Gcgr antagonist called compound 1 was shown to block glucagon-mediated glycogenolysis in human hepatocytes and perfused mouse liver (99). Furthermore, glucagon receptor antagonists such as Bay 27-9955 have been shown to block the actions of exogenous glucagon in normal human subjects (96). Hence, attenuation of glucagon receptor signaling represents an intriguing physiological approach for the treatment of type 2 diabetes.

GLP-1

Synthesis, secretion, and degradation

GLP-1 is a 30-amino-acid peptide hormone synthesized in two principal equipotent molecular forms, GLP-1-(7–36) amide and GLP-1-(7–37). After ingestion of nutrients, two periods of GLP-1 secretion can be identified: an early and a late phase. The early phase initiates within minutes of eating and may last for 30–60 min. The second phase is more prolonged, lasting 1–3 h after a meal (48, 63), and is probably attributable to direct interaction of digested luminal nutrients with L-cells. The early phase of GLP-1 secretion is likely regulated through a combination of neural and hormonal mediators, which remain poorly understood (44, 59, 100)

GLP-1 is rapidly inactivated and cleared from the circulation following secretion from gut L-cells. Bioactive intact GLP-1 undergoes enzymatic cleavage by the ubiquitously expressed serine protease dipeptidyl peptidase IV (DPP-IV). This enzyme cleaves at the penultimate alanine residue to produce an NH₂-terminally truncated product incapable of stimulating insulin release through the GLP-1 receptor (74, 87). The half-life of intact GLP-1 assessed following exogenous peptide administration is <2 min in rodents (74) and in normal and diabetic human subjects (35).

GLP-1 Action and the GLP-1R

GLP-1 potentiates glucose-stimulated insulin secretion and enhances insulin biosynthesis via induction of insulin gene expression (41, 51) (FIGURE 2). GLP-1 also stimulates somatostatin and inhibits glucagon secretion (94). GLP-1R activation increases β -cell mass through stimulation of β -cell proliferation and neogenesis and inhibition of apoptosis (39, 81). GLP-1 exerts these effects through a GPCR, a member of the glucagon-secretin receptor family (119) that is widely expressed in pancreatic islets, brain, heart, kidney, and gastrointestinal tract (27, 119). To date only one GLP-1R has been identified that transduces GLP-1's effects coupled to control of glucose homeostasis. Intriguingly, GLP-1 has been reported to improve insulin sensitivity, and various actions of GLP-1 on peripheral tis-

ues such as muscle, liver, and fat have been reported independently of the detection of the known GLP-1 receptor. Hence, the presence of functional GLP-1 receptors with different signaling properties in peripheral tissues such as muscle, fat, and liver remains a possibility.

GLP-1 stimulates adenylate cyclase and phospholipase C with subsequent activation of cAMP-dependent protein kinase A (PKA) and protein kinase C (PKC) leading to an increase in cytosolic calcium in both islet and nonislet cell lines (41, 64). GLP-1 increases insulin gene transcription in a PKA-independent manner (114). A role for cAMP guanine nucleotide exchange factors (GEFs) in downstream signaling from the GLP-1R in β -cells and more specifically for cAMP GEF II has also been demonstrated (71, 72). GLP-1 stimulates insulin gene expression through activation of nuclear factor of activated T-cells (NFAT) (80) and activation of ERK through a mechanism dependent on MEK but independent of both Raf and Ras (54).

The observation that GLP-1 stimulates β -cell proliferation and promotes β -cell survival has engendered much interest in the therapeutic potential of GLP-1R agonists for enhancing β -cell mass in human subjects with diabetes. GLP-1 increases cell proliferation, phosphoinositide 3-kinase, and PDX-1 in islet cell lines in a PKC- and epidermal growth factor receptor-dependent manner (22, 23, 24, 122). GLP-1R agonists also induce differentiation of pancreatic exocrine cells into an endocrine phenotype, as evidenced by increased expression of β -cell specific genes and develop-

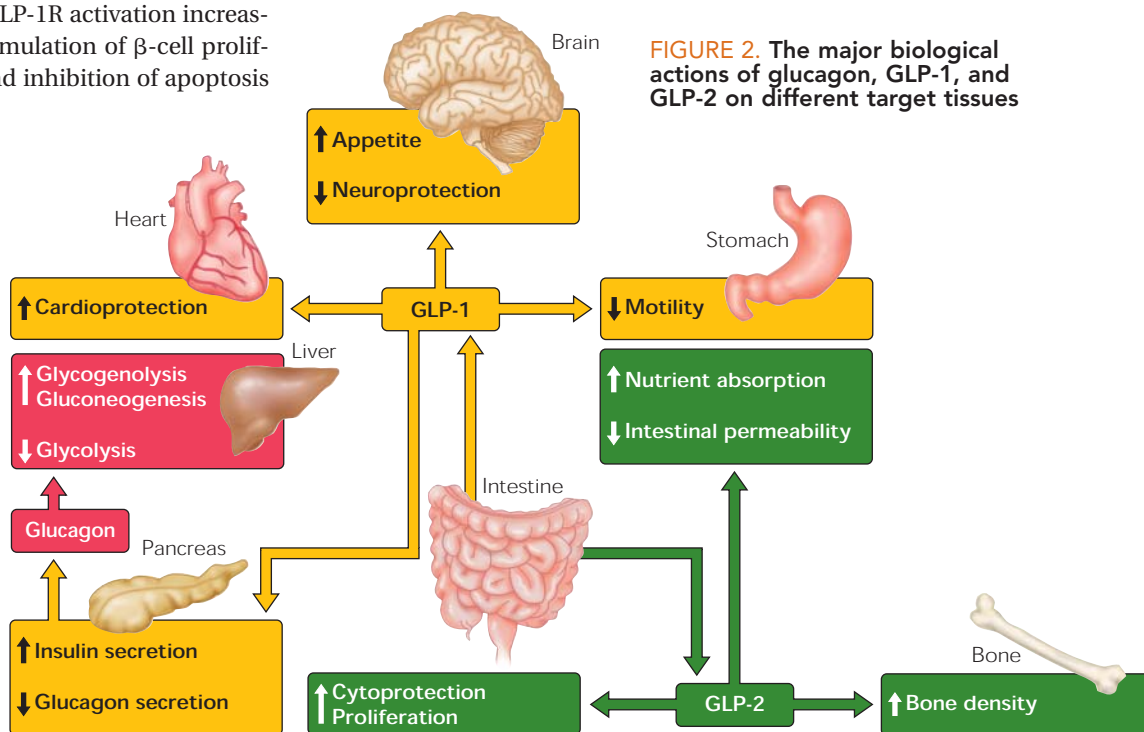


FIGURE 2. The major biological actions of glucagon, GLP-1, and GLP-2 on different target tissues





ment of glucose-stimulated insulin secretion (130). The mechanisms important for GLP-1R-dependent control of exocrine cell differentiation are incompletely understood but appear to involve signaling via bone morphogenic proteins and the TGF- β pathway (125).

Extrapancreatic actions of GLP-1

GLP-1 inhibits gastric emptying and increases satiety, leading to weight loss following chronic treatment with GLP-1R agonists (76). GLP-1 receptors have been localized to multiple regions of the brain, including the hypothalamus, which is known to regulate energy homeostasis (113). More recently, GLP-1 has been shown to exert effects on the heart in dogs and rodents. GLP-1 or exendin-4 increases blood pressure and heart rate in rats (10), and GLP-1R activation directly protects the heart against ischemia/reperfusion injury in the rat (13). Conversely GLP-1R $^{-/-}$ mice exhibit elevated left-ventricular end-diastolic pressure and increased left-ventricular thickness (55). Elimination or restoration of GLP-1 receptor signaling has also been shown to modify learning and enhance neuroprotection in rodents (46) (FIGURE 2).

The physiological importance of GLP-1 has been examined using GLP-1 receptor antagonists such as exendin-(9–39) and GLP-1R $^{-/-}$ mice. Administration of exendin-(9–39) to rats or human subjects reduces insulin secretion and increases gastric emptying and plasma levels of glucagon, leading to increased glycemic excursion following glucose loading. These findings illustrate the physiological importance of endogenous GLP-1

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for control of islet hormone release, gut motility, and glucose clearance (47, 104, 105). Similarly, GLP-1R $^{-/-}$ mice exhibit mild fasting hyperglycemia and glucose intolerance after either oral or intraperitoneal glucose loading, in association with defective glucose-stimulated insulin secretion (109). Moreover, GLP-1R $^{-/-}$ mice exhibit a reduction in the number of large islets, defective regeneration of β -cell mass following partial pancreatectomy, and increased susceptibility to β -cell apoptosis following streptozotocin administration (34, 81, 83). Hence, endogenous GLP-1 is essential for both β -cell function and the adaptive response to experimental islet injury.

GLP-1 Receptor Agonists and DPP-IV Inhibitors: Therapeutic Potential for the Treatment of Type 2 Diabetes

Pharmacological administration of GLP-1 in humans lowers blood glucose via stimulation of insulin secretion, suppression of glucagon release, and reduction of gastric emptying (57). Exendin-4, isolated from the venom of the gila monster *Heloderma suspectum*, is a potent GLP-1 receptor agonist that shares 53% amino acid identity with GLP-1 yet is resistant to DPP-IV cleavage (49). Exenatide (synthetic exendin-4), the first clinically approved GLP-1R agonist, lowered blood glucose in subjects with type 2 diabetes in both short-term and 30-wk clinical studies (21, 36, 73, 79). Exenatide injected twice daily in combination with metformin, sulfonylureas, or both oral agents significantly reduced levels of HbA1c and fasting glucose in association with modest degrees of weight loss in 6-mo pivotal studies (21, 36, 73). Given the success of Exenatide in lowering HbA1c and preventing weight gain, there is considerable effort underway to develop additional GLP-1R agonists with more prolonged durations of action.

Alternative strategies for prolonging the half-life of GLP-1 include coupling of degradation-resistant GLP-1 analogs to albumin (75) or the creation of a recombinant albumin-GLP-1 protein (7) to take advantage of the long circulating half-life of albumin in vivo. Liraglutide is a fatty-acylated GLP-1 analog that binds human serum albumin in a non-covalent manner. Liraglutide improves glucose control in human diabetic subjects after once-daily subcutaneous administration (37, 61, 84). CJC-1131 is a GLP-1 analog with a chemical linker attached to the COOH terminus allowing for covalent binding to albumin. CJC-1131 mimics the effects of native GLP-1 in vivo by stimulating insulin secretion and biosynthesis and by inhibiting food intake in a murine model of type 2 diabetes (75). CJC-1131 is currently being evaluated in phase II clinical trials for the treatment of type 2 diabetes. Albugon is a recombinant GLP-1-albumin protein that retains the ability to activate GLP-1R-dependent pathways coupled to reduction of blood glucose. Remarkably, Albugon rapidly reduces food intake and inhibits gastric emptying in preclinical studies within minutes of administration, suggesting that direct central nervous system penetration of GLP-1R agonists may not be required for GLP-1R-dependent actions in the brain (7).

DPP-IV and glucose homeostasis

An alternative to GLP-1R activation involves the inhibition of the activity of the enzyme DPP-IV responsible for the degradation of native GLP-1.

Genetic inactivation of the DPP-IV gene in mice or naturally occurring DPP-IV gene mutation in rats results in improved glucose tolerance, enhanced insulin secretion, and increased levels of intact bioactive GLP-1 (85, 90). DPP-IV inhibitors have been shown to improve glucose control in experimental models of diabetes (2, 9, 95). Inhibition of DPP-IV activity has also been shown to lower HbA1c levels in short-term studies in type 2 diabetics (1, 3). A number of DPP-IV inhibitors, including Vildagliptin and Sitagliptin, are currently being assessed in late-stage clinical trials. Most of these inhibitors reduce DPP-IV activity by 50–90% at 12–24 h after administration, with a concomitant two- to threefold increase in GLP-1 levels detected after meal ingestion in human subjects. Vildagliptin (LAF 237) has been shown to reduce fasting glucose levels throughout the day, predominantly via inhibition of glucagon levels and enhancement of glucose-stimulated insulin secretion. The long-term efficacy and safety of these agents in subjects with type 2 diabetes is not yet known.

GLP-2

Synthesis and secretion

GLP-2 is a 33-amino-acid peptide cosecreted with GLP-1, oxyntomodulin, and glicentin from enteroendocrine L-cells. Circulating levels of GLP-2 are low in the fasted state and increase following food intake (17, 124). GLP-2, like GLP-1, contains an alanine at position 2 and is inactivated by DPP-IV cleavage in rodents and humans (42, 62). Accordingly, bioactive intact GLP-2-(1–33) exhibits a short $t_{1/2}$ due to DPP-IV-mediated inactivation and renal clearance (103, 118). Cleavage of full length GLP-2-(1–33) generates the metabolite GLP-2-(3–33) that exhibits weak agonist and partial antagonist properties in rodents (112, 120).

The biological actions of GLP-2 were identified following studies of rodents with glucagon-producing tumors. Nude mice with subcutaneous glucagonomas exhibited significant bowel growth, and subsequent experiments demonstrated that the PGDP with potent intestinotrophic activity was GLP-2 (40). Blockade of endogenous GLP-2 using exogenous GLP-2-(30–33) reduced the extent of adaptive mucosal hyperplasia detected after fasting and refeeding in mice (112), implicating an essential role for GLP-2 in mucosal growth and apoptosis.

The GLP-2 receptor

The biological actions of GLP-2 are transduced through a single receptor of the class II glucagon-secretin family (88) with the GLP-2R sharing considerable sequence identity with GLP-1R and

glucagon receptors (86, 88). GLP-2R mRNA transcripts have been identified in the rodent stomach, intestine, brain, and lung (88, 128). More recent data using immunohistochemistry and in situ hybridization techniques has localized GLP-2R expression to human enteroendocrine cells, murine enteric neurons, and subepithelial myofibroblasts in rat, mouse, marmoset, and human intestine (12, 92, 128).

Activation of GLP-2 receptor signaling in heterologous cells expressing a transfected GLP-2R leads to increased intracellular cAMP, activation of PKA, an increase in cAMP-response element- and AP-1-dependent gene transcription, and increased immediate-early gene expression (88, 129). GLP-2R activation confers resistance to chemically-induced apoptosis in fibroblasts (15, 126) in association with reduced levels of activated glycogen synthase-3 (GSK-3), Bad, and Bax (127). Studies using human HeLa cells demonstrate that GLP-2R activation leads to increased levels of cAMP and ERK1/2 activation; however, GLP-2 enhances cytoprotection in HeLa cells in a PKA-dependent but ERK1/2-independent manner (78).

GLP-2 action and therapeutic potential

GLP-2 prevents or reduces mucosal epithelial damage in multiple experimental models of intestinal injury. Exogenous administration of a degradation-resistant GLP-2 analog h[Gly²]-GLP-2 enhanced the rate and magnitude of the intestinal adaptive response in rats with major small bowel resection (108). GLP-2 markedly enhanced survival and reduced bacterial translocation and gut injury in mice with nonsteroidal anti-inflammatory drug-induced enteritis (14). Similarly, GLP-2 prevented weight loss and reduced the severity of epithelial damage in mice with dextran sulfate-induced colitis (43). Moreover, GLP-2 exerts therapeutic actions in a wide number of preclinical models of gut injury, including chemotherapy-induced mucositis (15, 117), ischemia-reperfusion injury (97, 98), and genetic models of inflammatory bowel disease (4).

GLP-2 also exerts rapid actions independent of mucosal growth and cytoprotection, including stimulation of nutrient absorption (18, 28), inhibition of gut motility (123), reduction of intestinal permeability (11), and modulation of intestinal blood flow (56). GLP-2 enhances mucosal barrier function by both transcellular and paracellular pathways (11), and these actions are maintained in the setting of experimental intestinal inflammation or exogenous stress (25, 26).

GLP-2 may also exert its actions in the gut in the absence of enteral nutrition. Exogenous GLP-2 dose-dependently increased small intestine weight, DNA and protein content, and villus height in parenterally fed neonatal piglets (19). Similarly,



GLP-2 promoted gut mucosal growth in premature pigs maintained with parenteral nutrition by suppression of protein degradation and reduction of apoptosis. (20). The antiapoptotic actions of GLP-2 described in studies of cell lines *in vitro* resemble actions of GLP-2 in the injured gut *in vivo* (50). GLP-2 increased survival of intestinal epithelial cells in neonatal parenterally fed piglets in association with induction of protein kinase B (PKB) and GSK-3 phosphorylation and enhanced Bcl-2 expression (19). Intriguingly, the antiapoptotic actions of GLP-2 were more prominent in the gut epithelium at lower infusion doses ($2.5 \text{ nM} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$), whereas higher doses ($10 \text{ nM} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) of exogenous GLP-2 stimulated pathways coupled to cell proliferation (19).

The ability of GLP-2 to enhance nutrient absorption, increase the mucosal surface area, and promote intestinal epithelial survival has prompted examination of the actions of GLP-2 in human subjects with intestinal disorders, primarily short-bowel syndrome. GLP-2 improved intestinal absorption and nutritional status in a 5-wk pilot study of patients with short-bowel syndrome (terminal ileum and colon resected), with severe energy malabsorption (68). GLP-2 treatment increased body weight and energy retention in association with reduced nutrient loss, decreased bone resorption, and increased bone density in GLP-2-treated patients (58). A degradation-resistant GLP-2 analog, Teduglutide, is currently being examined in a phase II study of Crohn's disease and a phase II/III study of short-bowel syndrome. The results of these studies will provide some indication as to whether GLP-2 therapy will prove safe and effective for treatment of specific human intestinal disorders.

Conclusions

The structurally related PGDPs have generated increasing interest due to their pleiotropic biological properties as well as potential for the amelioration of common diseases such as diabetes and intestinal disorders. The development of receptor antagonists and mice with inactivating mutations in the PGDP receptors has facilitated elucidation of the essential physiological actions of these peptides in different tissues. Furthermore, both receptor agonists (glucagon, GLP-1, and GLP-2) and antagonists (glucagon) have been developed for the clinical treatment of human diseases. Taken together, the PGDPs represent an important group of related peptides essential for the control of cell proliferation, cytoprotection, and energy homeostasis. ■

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