Proglucagon-Derived Peptides: Mechanisms of Action and Therapeutic Potential

Elaine M Sinclair and Daniel J. Drucker

Physiology 20:357-365, 2005. doi:10.1152/physiol.00030.2005

Physiology (formerly published as News in Physiological Science) publishes brief review articles on major physiological developments. It is published bimonthly in February, April, June, August, October, and December by the American Physiological Society, 9650 Rockville Pike, Bethesda MD 20814-3991.
 ISSN: 1548-9213, ESSN: 1548-9221. Visit our website at http://www.the-aps.org/.

PHYSIOLOGY 20: 357–365, 2005; 10.1152/physiol.00030.2005

Proglucagon-Derived Peptides: Mechanisms of Action and Therapeutic Potential

Elaine M Sinclair
and Daniel J. Drucker

Department of Medicine, Banting and Best Diabetes Centre,
Toronto General Hospital and the University of Toronto,
Toronto, Ontario, Canada
d.drucker@utoronto.ca

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

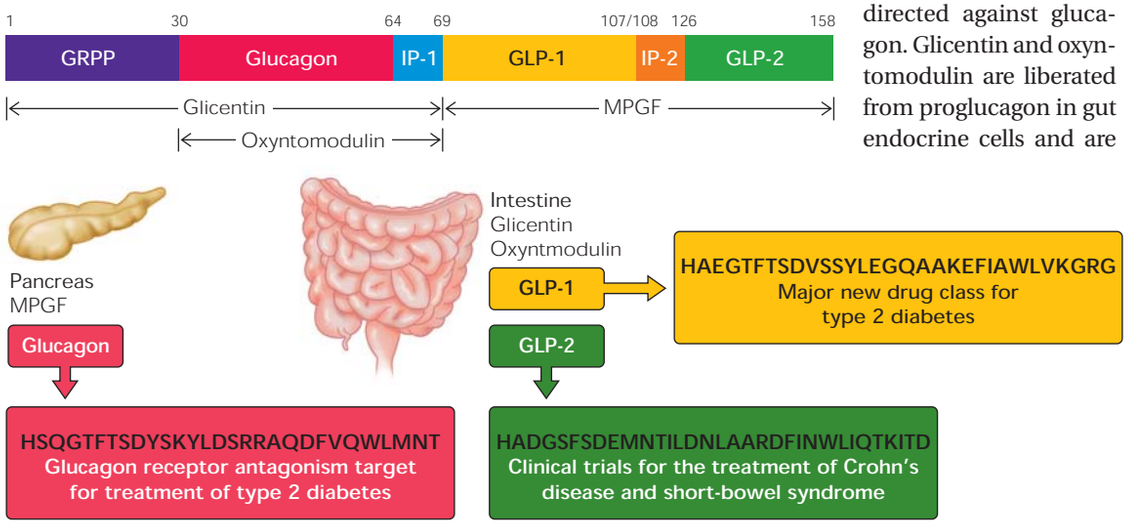

FIGURE 1. **Structural organization of proglucagon and the proglucagon-derived peptides**
Peptides liberated specifically in the pancreas or intestine are indicated below the full-length proglucagon sequence along with their amino acid sequence and therapeutic potential. The numerals above the proglucagon 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 NH_2-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 tissues 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-

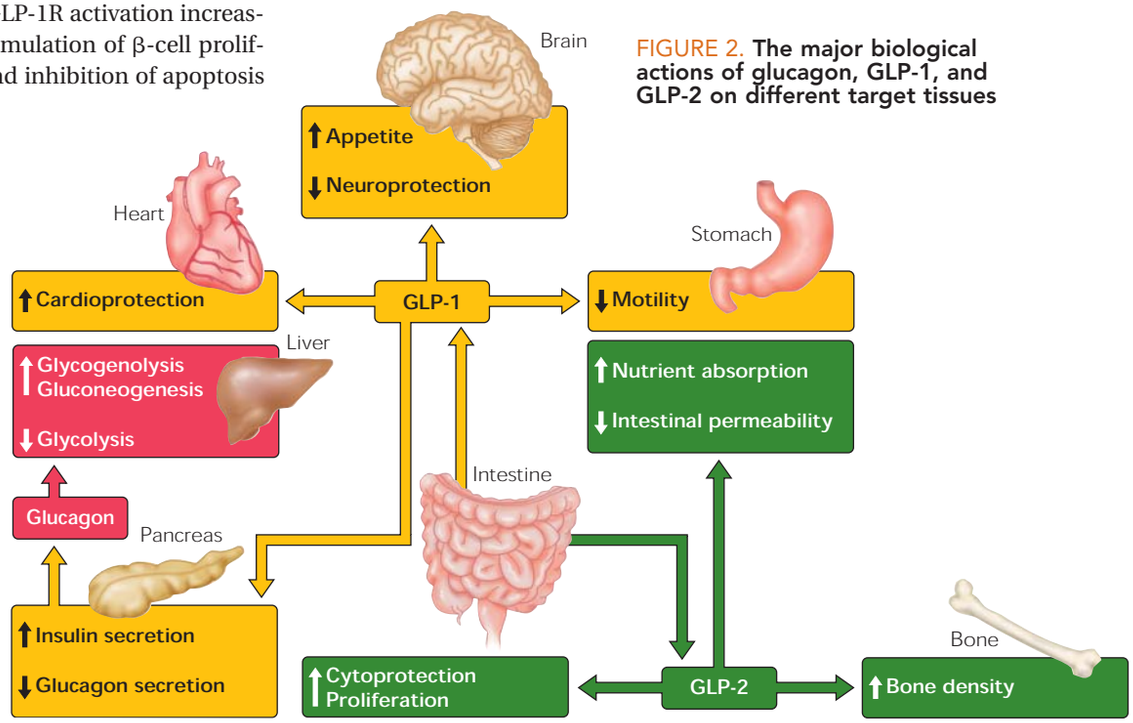

FIGURE 2. **The major biological actions of glucagon, GLP-1, and GLP-2 on different target tissues**

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 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.

"These findings illustrate the physiological importance of endogenous GLP-1 for control of islet hormone release, gut motility, and glucose clearance."

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 nM·kg^{-1}·day^{-1}), whereas higher doses (10 nM·kg^{-1}·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. ■

D. J. Drucker is supported by a Canada Research Chair in Regulatory Peptides and by operating grants from the Canadian Institutes for Health Research, the Canadian Diabetes Association, the Juvenile Diabetes Research Foundation, and the Ontario Research and Development Challenge Fund.

References

1. Ahren B, Gomis R, Standl E, Mills D, and Schweizer A. Twelve- and 52-week efficacy of the dipeptidyl peptidase IV inhibitor LAF237 in metformin-treated patients with type 2 diabetes. *Diabetes Care* 27: 2874–2880, 2004.
2. Ahren B, Holst JJ, Martensson H, and Balkan B. Improved glucose tolerance and insulin secretion by inhibition of dipeptidyl peptidase IV in mice. *Eur J Pharmacol* 404: 239–245, 2000.
3. Ahren B, Simonsson E, Larsson H, Landin-Olsson M, Torgeirsson H, Jansson PA, Sandqvist M, Bavenholm P, Efendic S, Eriksson JW, Dickinson S, and Holmes D. Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4-week study period in type 2 diabetes. *Diabetes Care* 25: 869–875, 2002.
4. Alavi K, Schwartz MZ, Palazzo JP, and Prasad R. Treatment of inflammatory bowel disease in a rodent model with the intestinal growth factor glucagon-like peptide-2. *J Pediatr Surg* 35: 847–851, 2000.
5. Anini Y, Jarrousse C, Chariot J, Nagain C, Yanaihara N, Sasaki K, Bernad N, Le Nguyen D, Bataille D, and Roze C. Oxyntomodulin inhibits pancreatic secretion through the nervous system in rats. *Pancreas* 20: 348–360, 2000.
6. Baggio LL, Huang Q, Brown TJ, and Drucker DJ. Oxyntomodulin and glucagon-like peptide-1 differentially regulate murine food intake and energy expenditure. *Gastroenterology* 127: 546–558, 2004.
7. Baggio LL, Huang Q, Brown TJ, and Drucker DJ. A recombinant human glucagon-like peptide (GLP)-1-albumin protein (albugon) mimics peptidergic activation of GLP-1 receptor-dependent pathways coupled with satiety, gastrointestinal motility, and glucose homeostasis. *Diabetes* 53: 2492–2500, 2004.
8. Baldissera FG, Holst JJ, Knuhtsen S, Hilsted L, and Nielsen OV. Oxyntomodulin (glicentin-(33—69)): pharmacokinetics, binding to liver cell membranes, effects on isolated perfused pig pancreas, and secretion from isolated perfused lower small intestine of pigs. *Regul Pept* 21: 151–166, 1988.
9. Balkan B, Kwasnik L, Miserendino R, Holst JJ, and Li X. Inhibition of dipeptidyl peptidase IV with NVP-DPP728 increases plasma GLP-1 (7-36 amide) concentrations and improves oral glucose tolerance in obese Zucker rats. *Diabetologia* 42: 1324–1331, 1999.
10. Barragan JM, Rodriguez RE, and Blazquez E. Changes in arterial blood pressure and heart rate induced by glucagon-like peptide-1-(7—36 amide) in rats. *Am J Physiol Endocrinol Metab* 266: E459–E466, 1994.
11. Benjamin MA, McKay DM, Yang PC, Cameron H, and Perdue MH. Glucagon-like peptide-2 enhances intestinal epithelial barrier function of both transcellular and paracellular pathways in the mouse. *Gut* 47: 112–119, 2000.
12. Bjerknes M and Cheng H. Modulation of specific intestinal epithelial progenitors by enteric neurons. *Proc Natl Acad Sci USA* 98: 12497–12502, 2001.
13. Bose AK, Mocanu MM, Carr RD, Brand CL, and Yellon DM. Glucagon-like peptide-1 (GLP-1) can directly protect the heart against ischemia/reperfusion injury. *Diabetes* 54: 146–151, 2005.
14. Boushey RP, Yusta B, and Drucker DJ. Glucagon-like peptide 2 decreases mortality and reduces the severity of indomethacin-induced murine enteritis. *Am J Physiol Endocrinol Metab* 277: E937–E947, 1999.
15. Boushey RP, Yusta B, and Drucker DJ. 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, 2001.
16. Brand CL, Rolin B, Jorgensen PN, Svendsen I, Kristensen JS, and Holst JJ. Immunoneutralization of endogenous glucagon with monoclonal glucagon antibody normalizes hyperglycaemia in moderately streptozotocin-diabetic rats. *Diabetologia* 37: 985–993, 1994.

17. Brubaker PL, Crivici A, Izzo A, Ehrlich P, Tsai CH, and Drucker DJ. Circulating and tissue forms of the intestinal growth factor, glucagon-like peptide-2. *Endocrinology* 138: 4837–4843, 1997.

18. Brubaker PL, Izzo A, Hill M, and Drucker DJ. Intestinal function in mice with small bowel growth induced by glucagon-like peptide-2. *Am J Physiol Endocrinol Metab* 272: E1050–E1058, 1997.

19. Burrin DG, Stoll B, Guan X, Cui L, Chang X, and Holst JJ. Glucagon-like peptide 2 dose-dependently activates intestinal cell survival and proliferation in neonatal piglets. *Endocrinology* 146: 22–32, 2005.

20. Burrin DG, Stoll B, Jiang R, Petersen Y, Elnif J, Buddington RK, Schmidt M, Holst JJ, Hartmann B, and Sangild PT. GLP-2 stimulates intestinal growth in premature TPN-fed pigs by suppressing proteolysis and apoptosis. *Am J Physiol Gastrointest Liver Physiol* 279: G1249–G1256, 2000.

21. Buse JB, Henry RR, Han J, Kim DD, Fineman MS, and Baron AD. Effects of exenatide (Exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 27: 2628–2635, 2004.

22. Buteau J, Foisy S, Joly E, and Prentki M. Glucagon-like peptide 1 induces pancreatic beta-cell proliferation via transactivation of the epidermal growth factor receptor. *Diabetes* 52: 124–132, 2003.

23. Buteau J, Foisy S, Rhodes CJ, Carpenter L, Biden TJ, and Prentki M. Protein kinase Czeta activation mediates glucagon-like peptide-1-induced pancreatic beta-cell proliferation. *Diabetes* 50: 2237–2243, 2001.

24. Buteau J, Roduit R, Susini S, and Prentki M. 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 beta (INS-1)-cells. *Diabetologia* 42: 856–864, 1999.

25. Cameron HL and Perdue MH. Stress impairs murine intestinal barrier function: improvement by glucagon-like peptide-2. *J Pharmacol Exp Ther* 314: 214–220, 2005.

26. Cameron HL, Yang PC, and Perdue MH. Glucagon-like peptide-2-enhanced barrier function reduces pathophysiology in a model of food allergy. *Am J Physiol Gastrointest Liver Physiol* 284: G905–G912, 2003.

27. Campos RV, Lee YC, and Drucker DJ. Divergent tissue-specific and developmental expression of receptors for glucagon and glucagon-like peptide-1 in the mouse. *Endocrinology* 134: 2156–2164, 1994.

28. Cheeseman CI and Tsang R. The effect of gastric inhibitory polypeptide and glucagon like peptides on intestinal hexose transport. *Am J Physiol Gastrointest Liver Physiol* 271: G477–G482, 1996.

29. Cohen MA, Ellis SM, Le Roux CW, Batterham RL, Park A, Patterson M, Frost GS, Ghatei MA, and Bloom SR. Oxyntomodulin suppresses appetite and reduces food intake in humans. *J Clin Endocrinol Metab* 88: 4696–4701, 2003.

30. Collie NL, Zhu Z, Jordan S, and Reeve JR Jr. Oxyntomodulin stimulates intestinal glucose uptake in rats. *Gastroenterology* 112: 1961–1970, 1997.

31. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 350: 2272–2279, 2004.

32. Cryer PE, Davis SN, and Shamoon H. Hypoglycemia in diabetes. *Diabetes Care* 26: 1902–1912, 2003.

33. Dakin CL, Gunn I, Small CJ, Edwards CM, Hay DL, Smith DM, Ghatei MA, and Bloom SR. Oxyntomodulin inhibits food intake in the rat. *Endocrinology* 142: 4244–4250, 2001.

34. De Leon DD, Deng S, Madani R, Ahima RS, Drucker DJ, and Stoffers DA. Role of endogenous glucagon-like peptide-1 in islet regeneration following partial pancreatectomy. *Diabetes* 52: 365–371, 2003.

35. Deacon CF, Nauck MA, Toft-Nielsen M, Pridal L, Willms B, and Holst JJ. Both subcutaneously and intravenously administered glucagon-like peptide 1 are rapidly degraded from the NH_2-terminus in type II diabetic patients and in healthy subjects. *Diabetes* 44: 1126–1131, 1995.

36. Defronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, and Baron AD. Effects of exenatide (Exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 28: 1092–1100, 2005.

37. Degn KB, Juhl CB, Sturis J, Jakobsen G, Brock B, Chandramouli V, Rungby J, Landau BR, and Schmitz O. One week's treatment with the long-acting glucagon-like peptide 1 derivative liraglutide (NN2211) markedly improves 24-h glycemia and alpha- and beta-cell function and reduces endogenous glucose release in patients with type 2 diabetes. *Diabetes* 53: 1187–1194, 2004.

38. Dhanvantari S, Seidah NG, and Brubaker PL. Role of prohormone convertases in the tissue-specific processing of proglucagon. *Mol Endocrinol* 10: 342–355, 1996.

39. Drucker DJ. Glucagon-like peptides: regulators of cell proliferation, differentiation, and apoptosis. *Mol Endocrinol* 17: 161–171, 2003.

40. Drucker DJ, Ehrlich P, Asa SL, and Brubaker PL. Induction of intestinal epithelial proliferation by glucagon-like peptide 2. *Proc Natl Acad Sci USA* 93: 7911–7916, 1996.

41. Drucker DJ, Philippe J, Mojsov S, Chick WL, and Habener JF. Glucagon-like peptide I stimulates insulin gene expression and increases cyclic AMP levels in a rat islet cell line. *Proc Natl Acad Sci USA* 84: 3434–3438, 1987.

42. Drucker DJ, Shi Q, Crivici A, Sumner-Smith M, Tavares W, Hill M, DeForest L, Cooper S, and Brubaker PL. Regulation of the biological activity of glucagon-like peptide 2 in vivo by dipeptidyl peptidase IV. *Nat Biotechnol* 15: 673–677, 1997.

43. Drucker DJ, Yusta B, Boushey RP, Deforest L, and Brubaker PL. Human [Gly2]-GLP-2 reduces the severity of colonic injury in a murine model of experimental colitis. *Am J Physiol Gastrointest Liver Physiol* 276: G79–G91, 1999.

44. Dube PE and Brubaker PL. Nutrient, neural and endocrine control of glucagon-like peptide secretion. *Horm Metab Res* 36: 755–760, 2004.

45. Dunphy JL, Taylor RG, and Fuller PJ. Tissue distribution of rat glucagon receptor and GLP-1 receptor gene expression. *Mol Cell Endocrinol* 141: 179–186, 1998.

46. During MJ, Cao L, Zuzga DS, Francis JS, Fitzsimons HL, Jiao X, Bland RJ, Klugmann M, Banks WA, Drucker DJ, and Haile CN. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. *Nat Med* 9: 1173–1179, 2003.

47. Edwards CM, Todd JF, Mahmoudi M, Wang Z, Wang RM, Ghatei MA, and Bloom SR. Glucagon-like peptide 1 has a physiological role in the control of postprandial glucose in humans: studies with the antagonist exendin 9—39. *Diabetes* 48: 86–93, 1999.

48. Elliott RM, Morgan LM, Tredger JA, Deacon S, Wright J, and Marks V. Glucagon-like peptide-1(7—36)amide and glucose-dependent insulinotropic polypeptide secretion in response to nutrient ingestion in man: acute post-prandial and 24-h secretion patterns. *J Endocrinol* 138: 159–166, 1993.

49. Eng J, Kleinman WA, Singh L, Singh G, and Raufman JP. Isolation and characterization of exendin 4, an exendin 3 analogue from *Heloderma suspectum* venom. *J Biol Chem* 267: 7402–7405, 1992.

50. Estall JL and Drucker DJ. Tales beyond the crypt: glucagon-like peptide-2 and cytoprotection in the intestinal mucosa. *Endocrinology* 146: 19–21, 2005.

51. Fehmann HC and Habener JF. Insulinotropic hormone glucagon-like peptide-I(7—37) stimulation of proinsulin gene expression and proinsulin biosynthesis in insulinoma βTC-1 cells. *Endocrinology* 130: 159–166, 1992.

52. Furuta M, Yano H, Zhou A, Rouille Y, Holst JJ, Carroll R, Ravazolla M, Orci L, Furuta H, and Steiner DF. Defective prohormone processing and altered pancreatic islet morphology in mice lacking active SPC2. *Proc Natl Acad Sci USA* 94: 6646–6651, 1999.

53. Gelling RW, Du XQ, Dichmann DS, Romer J, Huang H, Cui L, Obici S, Tang B, Holst JJ, Fledelius C, Johansen PB, Rossetti L, Jelicks LA, Serup P, Nishimura E, and Charron MJ. Lower blood glucose, hyperglucagonemia, and pancreatic {alpha} cell hyperplasia in glucagon receptor knockout mice. *Proc Natl Acad Sci USA* 100: 1438–1443, 2003.

54. Gomez E, Pritchard C, and Herbert TP. cAMP-dependent protein kinase and Ca^{2+} influx through L-type voltage-gated calcium channels mediate Raf-independent activation of extracellular regulated kinase in response to glucagon-like peptide-1 in pancreatic beta-cells. *J Biol Chem* 277: 48146–48151, 2002.

55. Gros R, You X, Baggio LL, Kabir MG, Sadi AM, Mungrue IN, Parker TG, Huang Q, Drucker DJ, and Husain M. Cardiac function in mice lacking the glucagon-like peptide-1 receptor. *Endocrinology* 144: 2242–2252, 2003.

56. Guan X, Stoll B, Lu X, Tappenden KA, Holst JJ, Hartmann B, and Burrin DG. GLP-2-mediated up-regulation of intestinal blood flow and glucose uptake is nitric oxide-dependent in TPN-fed piglets 1. *Gastroenterology* 125: 136–147, 2003.

57. Gutniak M, Orskov C, Holst JJ, Ahren B, and Efendic S. Antidiabetogenic effect of glucagon-like peptide-1 (7—36)amide in normal subjects and patients with diabetes mellitus. *N Engl J Med* 326: 1316–1322, 1992.

58. Haderslev KV, Jeppesen PB, Hartmann B, Thulesen J, Sorensen HA, Graff J, Hansen BS, Tofteng F, Poulsen SS, Madsen JL, Holst JJ, Staun M, and Mortensen PB. Short-term administration of glucagon-like peptide-2. Effects on bone mineral density and markers of bone turnover in short-bowel patients with no colon. *Scand J Gastroenterol* 37: 392–398, 2002.

59. Hansen L, Lampert S, Mineo H, and Holst JJ. Neural regulation of glucagon-like peptide-1 secretion in pigs. *Am J Physiol Endocrinol Metab* 287: E939–E947, 2004.

60. Hansen LH, Abrahamsen N, and Nishimura E. Glucagon receptor mRNA distribution in rat tissues. *Peptides* 16: 1163–1166, 1995.

61. Harder H, Nielsen L, Tu DT, and Astrup A. The effect of liraglutide, a long-acting glucagon-like peptide 1 derivative, on glycemic control, body composition, and 24-h energy expenditure in patients with type 2 diabetes. *Diabetes Care* 27: 1915–1921, 2004.

62. Hartmann B, Harr MB, Jeppesen PB, Wojdemann M, Deacon CF, Mortensen PB, and Holst JJ. In vivo and in vitro degradation of glucagon-like peptide-2 in humans. *J Clin Endocrinol Metab* 85: 2884–2888, 2000.

63. Herrmann C, Goke R, Richter G, Fehmann HC, Arnold R, and Goke B. Glucagon-like peptide-1 and glucose-dependent insulin-releasing polypeptide plasma levels in response to nutrients. *Digestion* 56: 117–126, 1995.

64. Holz GG, Leech CA, and Habener JF. Activation of a cAMP-regulated Ca^{2+}-signaling pathway in pancreatic b-cells by the insulinotropic hormone glucagon-like peptide-1. *J Biol Chem* 270: 17749–17757, 1995.

65. Jarrousse C, Audousset-Puech MP, Dubrasquet M, Niel H, Martinez J, and Bataille D. Oxyntomodulin (glucagon-37) and its C-terminal octapeptide inhibit gastric acid secretion. *FEBS Lett* 188: 81–84, 1985.

66. Jarrousse C, Bataille D, and Jeanrenaud B. A pure enteroglucagon, oxyntomodulin (glucagon 37), stimulates insulin release in perfused rat pancreas. *Endocrinology* 115: 102–105, 1984.

67. Jelinek LJ, Lok S, Rosenberg GB, Smith RA, Grant FJ, Biggs S, Bensch PA, Kuijper JL, Sheppard PO, Sprecher CA, O'Hara PJ, Foster D, Walker KM, Chen LHJ, Mckernan PA, and Kindsvogel W. Expression cloning and signaling properties of the rat glucagon receptor. *Science* 259: 1614–1616, 1993.

68. Jeppesen PB, Hartmann B, Thulesen J, Graff J, Lohmann J, Hansen BS, Tofteng F, Poulsen SS, Madsen JL, Holst JJ, and Mortensen PB. Glucagon-like peptide 2 improves nutrient absorption and nutritional status in short-bowel patients with no colon. *Gastroenterology* 120: 806–815, 2001.

69. Jiang G and Zhang BB. Glucagon and regulation of glucose metabolism. *Am J Physiol Endocrinol Metab* 284: E671–E678, 2003.

70. Johnson DG, Goebel CU, Hruby VJ, Bregman MD, and Trivedi D. Hyperglycemia of diabetic rats decreased by a glucagon receptor antagonist. *Science* 215: 1115–1116, 1982.

71. Kang G, Chepurny OG, and Holz GG. cAMP-regulated guanine nucleotide exchange factor II (Epac2) mediates Ca(2+)-induced Ca(2+) release in INS-1 pancreatic beta-cells. *J Physiol* 536: 375–385, 2001.

72. Kashima Y, Miki T, Shibasaki T, Ozaki N, Miyazaki M, Yano H, and Seino S. Critical role of cAMP-GEFII/Rim2 complex in incretin-potentiated insulin secretion. *J Biol Chem* 276: 46046–46053, 2001.

73. Kendall DM, Riddle MC, Rosenstock J, Zhuang D, Kim DD, Fineman MS, and Baron AD. Effects of exenatide (Exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 28: 1083–1091, 2005.

74. Kieffer TJ, McIntosh CH, and Pederson RA. Degradation of glucose-dependent insulinotropic polypeptide and truncated glucagon-like peptide 1 in vitro and in vivo by dipeptidyl peptidase IV. *Endocrinology* 136: 3585–3596, 1995.

75. Kim JG, Baggio LL, Bridon DP, Castaigne JP, Robitaille MF, Jette L, Benquet C, and Drucker DJ. 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, 2003.

76. Kinzig KP, D'Alessio DA, and Seeley RJ. The diverse roles of specific GLP-1 receptors in the control of food intake and the response to visceral illness. *J Neurosci* 22: 10470–10476, 2002.

77. Kirkegaard P, Moody AJ, Holst JJ, Loud FB, Olsen PS, and Christiansen J. Glicentin inhibits gastric acid secretion in the rat. *Nature* 297: 156–157, 1982.

78. Koehler JA, Yusta B, and Drucker DJ. The HeLa cell glucagon-like peptide-2 receptor is coupled to regulation of apoptosis and ERK1/2 activation through divergent signaling pathways. *Mol Endocrinol* 19: 459–473, 2005.

79. Kolterman OG, Buse JB, Fineman MS, Gaines E, Heintz S, Bicsak TA, Taylor K, Kim D, Aisporna M, Wang Y, and Baron AD. Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. *J Clin Endocrinol Metab* 88: 3082–3089, 2003.

80. Lawrence MC, Bhatt HS, and Easom RA. NFAT regulates insulin gene promoter activity in response to synergistic pathways induced by glucose and glucagon-like peptide-1. *Diabetes* 51: 691–698, 2002.

81. Li Y, Hansotia T, Yusta B, Ris F, Halban PA, and Drucker DJ. Glucagon-like peptide-1 receptor signaling modulates beta cell apoptosis. *J Biol Chem* 278: 471–478, 2003.

82. Liang Y, Osborne MC, Monia BP, Bhanot S, Gaarde WA, Reed C, She P, Jetton TL, and Demarest KT. Reduction in glucagon receptor expression by an antisense oligonucleotide ameliorates diabetic syndrome in db/db mice. *Diabetes* 53: 410–417, 2004.

83. Ling Z, Wu D, Zambre Y, Flamez D, Drucker DJ, Pipeleers DG, and Schuit FC. Glucagon-like peptide 1 receptor signaling influences topography of islet cells in mice. *Virchows Arch* 438: 382–387, 2001.

84. Madsbad S, Schmitz O, Ranstam J, Jakobsen G, and Matthews DR. Improved glycemic control with no weight increase in patients with type 2 diabetes after once-daily treatment with the long-acting glucagon-like peptide 1 analog liraglutide (NN2211): a 12-week, double-blind, randomized, controlled trial. *Diabetes Care* 27: 1335–1342, 2004.

85. Marguet D, Baggio L, Kobayashi T, Bernard AM, Pierres M, Nielsen PF, Ribel U, Watanabe T, Drucker DJ, and Wagtmann N. Enhanced insulin secretion and improved glucose tolerance in mice lacking CD26. *Proc Natl Acad Sci USA* 97: 6874–6879, 2000.

86. Mayo KE, Miller LJ, Bataille D, Dalle S, Goke B, Thorens B, and Drucker DJ. International Union of Pharmacology. XXXV. The Glucagon Receptor Family. *Pharmacol Rev* 55: 167–194, 2003.

87. Mentlein R, Dahms P, Grandt D, and Kruger R. Proteolytic processing of neuropeptide Y and peptide YY by dipeptidyl peptidase IV. *Regul Pept* 49: 133–144, 1993.

88. 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, and Crivici A. Prototypic G protein-coupled receptor for the intestinotrophic factor glucagon-like peptide 2. *Proc Natl Acad Sci USA* 96: 1569–1573, 1999.

89. Myojo S, Tsujikawa T, Sasaki M, Fujiyama Y, and Bamba T. Trophic effects of glicentin on rat small-intestinal mucosa in vivo and in vitro. *J Gastroenterol* 32: 300–305, 1997.

90. Nagakura T, Yasuda N, Yamazaki K, Ikuta H, Yoshikawa S, Asano O, and Tanaka I. Improved glucose tolerance via enhanced glucose-dependent insulin secretion in dipeptidyl peptidase IV-deficient Fischer rats. *Biochem Biophys Res Commun* 284: 501–506, 2001.

91. Ohneda A, Ohneda K, Nagasaki T, and Sasaki K. Insulinotropic action of human glicentin in dogs. *Metabolism* 44: 47–51, 1995.

92. Orskov C, Hartmann B, Poulsen SS, Thulesen J, Hare KJ, and Holst JJ. GLP-2 stimulates colonic growth via KGF, released by subepithelial myofibroblasts with GLP-2 receptors. *Regul Pept* 124: 105–112, 2005.

93. Orskov C, Holst JJ, Knuhtsen S, Baldissera FGA, Poulsen SS, and Nielsen OV. Glucagon-like peptides GLP-1 and GLP-2, predicted products of the glucagon gene, are secreted separately from pig small intestine but not pancreas. *Endocrinology* 119: 1467–1475, 1986.

94. Orskov C, Holst JJ, and Nielsen OV. Effect of truncated glucagon-like peptide-1 [proglucagon-(78-107) amide] on endocrine secretion from pig pancreas, antrum, and nonantral stomach. *Endocrinology* 123: 2009–2013, 1988.

95. Pederson RA, White HA, Schlenzig D, Pauly RP, McIntosh CH, and Demuth HU. Improved glucose tolerance in Zucker fatty rats by oral administration of the dipeptidyl peptidase IV inhibitor isoleucine thiazolidide. *Diabetes* 47: 1253–1258, 1998.

96. Petersen KF and Sullivan JT. Effects of a novel glucagon receptor antagonist (Bay 27-9955) on glucagon-stimulated glucose production in humans. *Diabetologia* 44: 2018–2024, 2001.

97. Prasad R, Alavi K, and Schwartz MZ. GLP-2alpha accelerates recovery of mucosal absorptive function after intestinal ischemia/reperfusion. *J Pediatr Surg* 36: 570–572, 2001.

98. Prasad R, Alavi K, and Schwartz MZ. Glucagonlike peptide-2 analogue enhances intestinal mucosal mass after ischemia and reperfusion. *J Pediatr Surg* 35: 357–359, 2000.

99. Qureshi SA, Rios Candelore M, Xie D, Yang X, Tota LM, Ding VD, Li Z, Bansal A, Miller C, Cohen SM, Jiang G, Brady E, Saperstein R, Duffy JL, Tata JR, Chapman KT, Moller DE, and Zhang BB. A novel glucagon receptor antagonist inhibits glucagon-mediated biological effects. *Diabetes* 53: 3267–3273, 2004.

100. Rocca AS and Brubaker PL. Role of the vagus nerve in mediating proximal nutrient-induced glucagon- like peptide-1 secretion. *Endocrinology* 140: 1687–1694, 1999.

101. Rothenberg ME, Eilertson CD, Klein K, Zhou Y, Lindberg I, McDonald JK, Mackin RB, and Noe BD. Processing of mouse proglucagon by recombinant prohormone convertase 1 and immunopurified prohormone convertase 2 in vitro. *J Biol Chem* 270: 10136–10146, 1995.

102. Rouille Y, Westermark G, Martin SK, and Steiner DF. Proglucagon is processed to glucagon by prohormone convertase PC2 in aTC1-6 cells. *Proc Natl Acad Sci USA* 91: 3242–3246, 1994.

103. Ruiz-Grande C, Pintado J, Alarcon C, Castilla C, Valverde I, and Lopez-Novoa JM. Renal catabolism of human glucagon-like peptides 1 and 2. *Can J Physiol Pharmacol* 68: 1568–1573, 1990.

104. Schirra J, Nicolaus M, Roggel R, Katschinski M, Storr M, Woerle HJ, and Goke B. Endogenous GLP-1 controls endocrine pancreatic secretion and antro-pyloro-duodenal motility in humans. *Gut*. In press.

105. Schirra J, Sturm K, Leicht P, Arnold R, Goke B, and Katschinski M. Exendin(9—39)amide is an antagonist of glucagon-like peptide-1(7—36)amide in humans. *J Clin Invest* 101: 1421–1430, 1998.

106. Schjoldager B, Mortensen PE, Myhre J, Christiansen J, and Holst JJ. Oxyntomodulin from distal gut. Role in regulation of gastric and pancreatic functions. *Dig Dis Sci* 34: 1411–1419, 1989.

107. Schjoldager BTG, Baldissera FGA, Mortensen PE, Holst JJ, and Christiansen J. Oxyntomodulin: A potential hormone from the distal gut. Pharmacokinetics and effects on gastric acid and insulin secretion in man. *Eur J Clin Invest* 18: 499–503, 1988.

108. Scott RB, Kirk D, MacNaughton WK, and Meddings JB. GLP-2 augments the adaptive response to massive intestinal resection in rat. *Am J Physiol Gastrointest Liver Physiol* 275: G911–G921, 1998.

109. Scrocchi LA, Brown TJ, MacLusky N, Brubaker PL, Auerbach AB, Joyner AL, and Drucker DJ. Glucose intolerance but normal satiety in mice with a null mutation in the glucagon-like peptide receptor gene. *Nat Med* 2: 1254–1258, 1996.

110. Shah P, Vella A, Basu A, Basu R, Schwenk WF, and Rizza RA. Lack of suppression of glucagon contributes to postprandial hyperglycemia in subjects with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 85: 4053–4059, 2000.

111. Shibata C, Naito H, Jin XL, Ueno T, Funayama Y, Fukushima K, Hashimoto A, Matsuno S, and Sasaki I. Effect of glucagon, glicentin, glucagon-like peptide-1 and -2 on interdigestive gastroduodenal motility in dogs with a vagally denervated gastric pouch. *Scand J Gastroenterol* 36: 1049–1055, 2001.

112. Shin ED, Estall JL, Izzo A, Drucker DJ, and Brubaker PL. Mucosal adaptation to enteral nutrients is dependent on the physiologic actions of glucagon-like peptide-2 in mice. *Gastroenterology* 128: 1340–1353, 2005.

113. Shughrue PJ, Lane MV, and Merchenthaler I. Glucagon-like peptide-1 receptor (GLP1-R) mRNA in the rat hypothalamus. *Endocrinology* 137: 5159–5162, 1996.

114. Skoglund G, Hussain MA, and Holz GG. Glucagon-like peptide 1 stimulates insulin gene promoter activity by protein kinase A-independent activation of the rat insulin I gene cAMP response element. *Diabetes* 49: 1156–1164, 2000.

115. Sloop KW, Cao JX, Siesky AM, Zhang HY, Bodenmiller DM, Cox AL, Jacobs SJ, Moyers JS, Owens RA, Showalter AD, Brenner MB, Raap A, Gromada J, Berridge BR, Monteith DK, Porksen N, McKay RA, Monia BP, Bhanot S, Watts LM, and Michael MD. Hepatic and glucagon-like peptide-1-mediated reversal of diabetes by glucagon receptor antisense oligonucleotide inhibitors. *J Clin Invest* 113: 1571–1581, 2004.

116. Svoboda M, Tastenoy M, Vertongen P, and Robberecht P. Relative quantitative analysis of glucagon receptor mRNA in rat tissues. *Mol Cell Endocrinol* 105: 131–137, 1994.

117. Tavakkolizadeh A, Shen R, Abraham P, Kormi N, Seifert P, Edelman ER, Jacobs DO, Zinner MJ, Ashley SW, and Whang EE. Glucagon-like peptide 2: a new treatment for chemotherapy-induced enteritis. *J Surg Res* 91: 77–82, 2000.

118. Tavares W, Drucker DJ, and Brubaker PL. Enzymatic- and renal-dependent catabolism of the intestinotropic hormone glucagon-like peptide-2 in rats. *Am J Physiol Endocrinol Metab* 278: E134–E139, 2000.

119. Thorens B, Porret A, BŸhler L, Deng SP, Morel P, and Widmann C. Cloning and functional expression of the human islet GLP-1 receptor: demonstration that exendin-4 is an agonist and exendin-(9—39) an antagonist of the receptor. *Diabetes* 42: 1678–1682, 1993.

120. Thulesen J, Knudsen LB, Hartmann B, Hastrup S, Kissow H, Jeppesen PB, Orskov C, Holst JJ, and Poulsen SS. The truncated metabolite GLP-2 (3—33) interacts with the GLP-2 receptor as a partial agonist. *Regul Pept* 103: 9–15, 2002.

121. Unger RH and Orci L. The essential role of glucagon in the pathogenesis of diabetes mellitus. *Lancet* 1: 14–16, 1975.

122. Wang H, Iezzi M, Theander S, Antinozzi PA, Gauthier BR, Halban PA, and Wollheim CB. Suppression of Pdx-1 perturbs proinsulin processing, insulin secretion and GLP-1 signalling in INS-1 cells. *Diabetologia* 48: 720–731, 2005.

123. Wojdemann M, Wettergren A, Hartmann B, and Holst JJ. Glucagon-like peptide-2 inhibits centrally induced antral motility in pigs. *Scand J Gastroenterol* 33: 828–832, 1998.

123a. Wynne K, Park AJ, Small CJ, Patterson M, Ellis SM, Murphy KG, Wren AM, Frost GS, Meeran K, Ghatei MA, and Bloom SR. Subcutaneous oxyntomodulin reduces body weight in overweight and obese subjects: a double-blind, randomized, controlled trial. *Diabetes* 54: 2390–2395, 2005.

124. Xiao Q, Boushey RP, Drucker DJ, and Brubaker PL. Secretion of the intestinotropic hormone glucagon-like peptide 2 is differentially regulated by nutrients in humans. *Gastroenterology* 117: 99–105, 1999.

125. Yew KH, Hembree M, Prasadan K, Preuett B, McFall C, Benjes C, Crowley A, Sharp S, Tulachan S, Mehta S, Tei E, and Gittes G. Crosstalk between BMP and TGF-beta signaling is essential for exendin-4 induced insulin-positive differentiation of AR42J cells. *J Biol Chem*. In press.

126. Yusta B, Boushey RP, and Drucker DJ. 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, 2000.

127. Yusta B, Estall J, and Drucker DJ. GLP-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, 2002.

128. Yusta B, Huang L, Munroe D, Wolff G, Fantaske R, Sharma S, Demchyshyn L, Asa SL, and Drucker DJ. Enteroendocrine localization of GLP-2 receptor expression. *Gastroenterology* 119: 744–755, 2000.

129. Yusta B, Somwar R, Wang F, Munroe D, Grinstein S, Klip A, and Drucker DJ. 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, 1999.

130. Zhou J, Wang X, Pineyro MA, and Egan JM. Glucagon-like peptide 1 and exendin-4 convert pancreatic AR42J cells into glucagon- and insulin-producing cells. *Diabetes* 48: 2358–2366, 1999.