Glucagon-like peptide 2: an update

Eric D. Shin[a], Daniel J. Drucker[b,c] and Patricia L. Brubaker[a,b]

Purpose of review

Glucagon-like peptide 2 (GLP-2) is a 33-amino acid peptide secreted in a nutrient-dependent manner from gut enteroendocrine cells. The proliferative and antiapoptotic actions of GLP-2 lead to expansion of the mucosal surface area and enhanced capacity for nutrient absorption in multiple models of experimental intestinal injury. These findings have raised the possibility that GLP-2 administration may produce therapeutic benefit in humans with intestinal insufficiency.

Recent findings

The actions of GLP-2 appear restricted to the gastrointestinal tract, central nervous system, and skeleton. GLP-2 exerts its effects through a G-protein–coupled receptor expressed in enteric neurons or enteroendocrine cells, suggesting that many of its actions are likely indirect through as yet unidentified secondary mediators. Exogenous administration of GLP-2 to mice, rats, or pigs reduces morbidity associated with intestinal damage and improves the structure and function of the intestinal mucosa. GLP-2 also exerts anabolic actions in bone via prevention of resorption. GLP-2 may also act in the brain to enhance neuronal survival via direct antiapoptotic actions. The cytoprotective and proliferative actions of GLP-2 highlight the need for further information on the efficacy and safety of long-term administration of GLP-2 in human subjects.

Summary

The available evidence suggests that GLP-2 upregulates pathways promoting restoration of intestinal barrier and absorptive function, leading to reduced bacterial translocation, improved nutrient uptake, and enhanced energy absorption. Degradation-resistant GLP-2 analogues are currently being tested in human clinical trials of subjects with inflammatory bowel disease and short bowel syndrome. Hence, GLP-2 may ultimately be used as a therapeutic agent for the treatment of metabolic disorders characterized by insufficient nutrient absorption.

Keywords

apoptosis, GLP-2, growth, intestine, proglucagon, proliferation, receptor, short bowel syndrome, signaling, therapeutic

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[a]Department of Physiology, University of Toronto, Toronto, Ontario, Canada; [b]Department of Medicine, University of Toronto, Toronto, Ontario, Canada; and [c]Banting and Best Diabetes Centre, University of Toronto, Toronto, Ontario, Canada

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D. J. D. is a consultant to NPS Pharmaceuticals.

Correspondence to Patricia L. Brubaker, Room 3366, Medical Sciences Building, University of Toronto, 1 King's College Circle, Toronto, ON M5S 1A8, Canada
Tel: 416-978-2593; fax: 416-978-2593; e-mail: p.brubaker@utoronto.ca

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Abbreviations

BHK	baby hamster kidney
cAMP	cyclic AMP
CNS	central nervous system
CRE	cyclic AMP response element
GLP	glucagon-like peptide
GLP-2R	glucagon-like peptide 2 receptor
MAPK	mitogen-activated protein kinase
PC	prohormone convertase
PGDP	proglucagon-derived peptide
PKA	protein kinase A
SBS	short bowel syndrome

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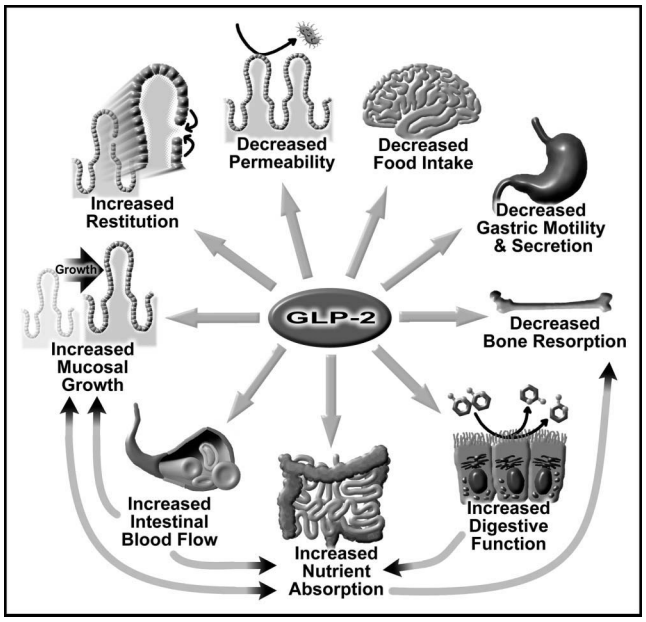
Introduction

Glucagon-like peptide 2 (GLP-2) is a 33-amino acid peptide derived from proglucagon that has been predominantly characterized by its ability to induce intestinal growth. Initial reports suggesting an intestinotropic role for one of the proglucagon-derived peptides (PGDPs) originated from two patients with proglucagon-producing tumors who had grossly enlarged small intestines [1,2]. Although proglucagon is expressed in the pancreas, intestine, and brain, circulating levels of the intestinal PGDPs correlated with gut adaptation in response to nutritional deprivation or excess, and intestinal resection or injury [3]. However, it was not until 1996 that GLP-2 was identified as the specific PGDP that stimulates intestinal growth *in vivo* [4]. GLP-2 is now known to induce growth in the intestine via enhancement of crypt cell proliferation and inhibition of enterocyte apoptosis (Fig. 1). However, a plethora of related actions have also been ascribed to this peptide, including inhibition of gastric motility and secretion, stimulation of digestive enzyme activity and nutrient transport, increased blood flow, enhanced epithelial barrier function, decreased bacterial translocation, and restitution of injured epithelium. Several recently described extraintestinal effects of GLP-2 include an anabolic shift in bone homeostasis, neuroprotective effects in the central nervous system (CNS), and centrally induced inhibition of food intake. An overview of GLP-2 action may be found in several excellent reviews [5,6•,7,8]. The focus of this article is the most recent and important advances

Figure 1. Schematic of the different biologic effects of exogenous glucagon-like peptide 2 treatment *in vivo*



Note that the effects on food intake have been reported only with glucagon-like peptide 2 given directly into the CNS.

in understanding of the mechanisms underlying GLP-2 synthesis, secretion, metabolism, signaling, and biologic actions, and the therapeutic potential of this intestinotropic peptide.

Glucagon-like peptide 2 synthesis, secretion, and metabolism

Understanding of the factors that regulate proglucagon gene expression is relatively sparse (reviewed in [8]). A single proglucagon gene is transcribed, leading to generation of an identical proglucagon precursor in pancreas, brain, and the gastrointestinal tract. Several cis-acting regulatory factors have been identified in the proximal proglucagon promoter, including the pancreatic α-cell promoter elements G1–G4 [9,10], a cyclic AMP (cAMP) response element (CRE) [11], an intestinal specific element referred to as the *glucagon upstream promoter* [12], and, most recently, a CRE-like 1 element [13]. However, only Pax6 [14,15], Cdx2/3 [16], Foxa1 [17], Foxa2 [18,19], and the Wnt signaling pathway [20] appear to be candidate regulators of proglucagon gene expression in the intestine.

Intestinal proglucagon mRNA levels decrease with fasting, whereas refeeding rapidly increases gene expression [21–25]. Intestinal proglucagon mRNA levels also increase during adaptive intestinal growth in association with alterations in nutrient intake [25,26]. Although the exact nutritional constituents that mediate changes in proglucagon expression remain largely unknown, peptones (intestinal luminal dietary protein) stimulate proglucagon gene expression [13,23] through both the CRE and the CRE-like 1 cis domains [13]. Additionally, dietary fiber and short-chain fatty acids enhance intestinal proglucagon expression in rodents through poorly understood mechanisms [21,24,25,27]. Furthermore, levels of intestinal proglucagon mRNA are generally found to be greater during fetal/neonatal life than in the adult [28].

Proglucagon is processed by prohormone convertase (PC) 1/3 in intestinal L cells to generate the intestinal PGDPs, including GLP-2, whereas cleavage by PC2, and possibly another enzyme, liberates glucagon in the pancreatic α cells [29–36]. Importantly, recent studies provide a more comprehensive understanding of PC action on proglucagon, because PC1/3 knockout mice exhibit diminished GLP-2 levels [37,38•], whereas PC2-deficient mice lack mature glucagon [31,39]. Lack of PC1/3 is also associated with intestinal dysfunction in the form of a mild diarrhea. Consistent with findings in mutant rodents, two human subjects deficient in functional PC1/3 exhibited defects in small intestinal absorptive function ranging from mild malabsorption to severe refractory neonatal diarrhea [40•]. Thus, the available evidence suggests that PC1/3 plays a critical role in the cleavage of proglucagon to form GLP-2 in the intestinal L cell and, further, that GLP-2 deficiency may be associated with intestinal dysfunction.

Glucagon-like peptide 2 secretion from the L cell is regulated by nutritional, hormonal, and neural factors. The primary stimulus for GLP-2 secretion is enteral nutrient intake, especially carbohydrate and fats [21,22,41–44]. Despite the fact that a meal rich in protein has no effect on GLP-2 secretion *in vivo* [42], protein hydrolysates enhance intestinal release of the PGDPs in the perfused rat ileum model [23]. Consistent with these findings, a very recent study has demonstrated that glutamine potently stimulates PGDP secretion from the intestinal L cell [45]. Additionally, short-chain fatty acids, either alone or as generated from bacterial fermentation of dietary fiber, stimulate GLP-2 secretion [24–26,46]. These findings provide a possible mechanistic explanation for the tropic effects of both glutamine and fiber, via stimulation of GLP-2 secretion, on the intestine [47].

Oral feeding in humans increases GLP-2 release in a biphasic pattern characterized by a rapid peak within 15 minutes and a second increase after approximately 1 hour [42,48]. Although the later peak has been attributed to direct effects of the luminal nutrients on the L cell, the early peak precedes contact of the nutrients with the L cell, leading to the suggestion that a neuro/endocrine mediator from the proximal gut indirectly activates the L cell after nutrient ingestion [49]. Hence, in rats and pigs, the presence of fat in the duodenum stimulates GIP secretion from duodenal K cells [50–52], which then stimulates the

release of GLP-2 from the distal regions of the small intestine through activation of the vagus nerve [51–54]. Consistent with these findings, functional muscarinic receptors have been demonstrated on the human L cell [55], although no endocrine modulator of the human L-cell response to nutrient ingestion has been reported to date. Nonetheless, it appears that postprandial GLP-2 secretion is regulated in a complex manner in humans and rodents, consisting of both direct (via nutrients) and indirect (via endocrine and/or neural) pathways.

Once released into the circulation, GLP-$2^{1\text{-}33}$ is rapidly metabolized by the ubiquitous enzyme dipeptidylpeptidase IV to produce the inactive metabolite GLP-$2^{3\text{-}33}$ [42,56–58]. Although GLP-$2^{3\text{-}33}$ is biologically inactive when injected into rodents [58,59], several recent reports have demonstrated that this peptide can function as a partial agonist at the GLP-2 receptor (GLP-2R) when injected at supraphysiologic concentrations [60] but can antagonize the intestinotropic actions of endogenous GLP-2 when administered at more physiologically relevant levels [61]. Development of functional GLP-2R antagonists will spur more detailed mechanistic studies of the physiologic roles of endogenous GLP-2.

Glucagon-like peptide 2 receptor

The GLP-2R is a 7-transmembrane–spanning G-protein–coupled receptor belonging to the class II glucagon/GIP receptor family [62]. A single gene at chromosome 17p13.3 encodes for the human GLP-2R, which has approximately 80% amino acid identity with the rat GLP-2R [62]. GLP-2R expression is tissue-specific, with highest levels in the jejunum, followed by the duodenum, ileum, colon, stomach, and brain, including the thalamus, hypothalamus, hippocampus, cerebral cortex, hindbrain, and brainstem [62–67,68•]. In addition, primary cultured rat astrocytes have been reported to express the GLP-2R [67]. The GLP-2R exhibits no significant binding of other members of the highly related glucagon superfamily [62,69,70].

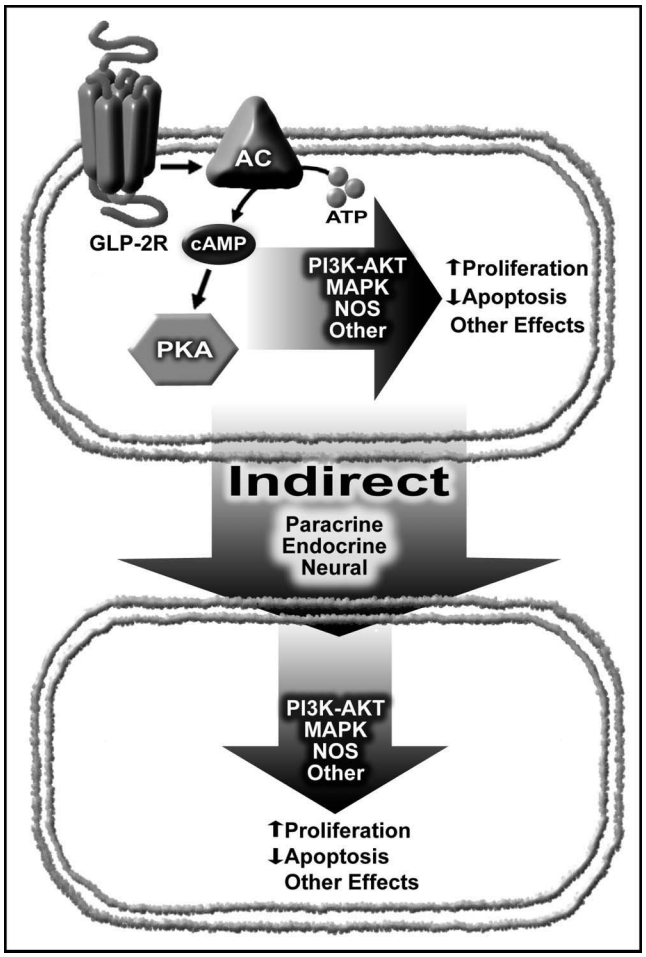
In the rat and pig intestine, GLP-2R mRNA is expressed at high levels in the fetus and early neonatal life, but declines toward postnatal levels with weaning [28,71,72]. Although these changes are likely coupled to nutrient ingestion, the exact factors that determine GLP-2R gene expression remain to be determined. Furthermore, recent studies examining expression of the GLP-2R mRNA in the CNS have demonstrated even more complex regulation, with different regions of the brain exhibiting varying expression profiles throughout development in the rat [68].

The exact cellular distribution of the GLP-2R within the gastrointestinal tract remains controversial. Immunoreactive GLP-2R was localized to a subset of enteroendocrine cells in the human intestinal epithelium [63]. However, using an *in situ* hybridization approach, GLP-2R mRNA was detected in enteric neurons of the mouse [73], whereas a recent report using the same technique localized GLP-2R expression to subepithelial cells in the lamina propria of rats [74]. Although the precise cellular localization of GLP-2R expression requires additional study, the available evidence suggests that many of the actions of GLP-2 may be exerted indirectly through secondary mediators, such as locally produced growth factors from enteroendocrine, neural, and/or the lamina propria cells (Fig. 2). In agreement with this hypothesis, a recent study has demonstrated that immunoneutralization of TGF-β abrogates the ability of GLP-2 to enhance wound healing *in vitro* [75•]. Similarly, a recent report has indicated that GLP-2 stimulates both the synthesis and secretion of insulin-like growth factor 1 by the intestine [76]. Further studies are clearly necessary to determine which, if any, of the biologic actions of GLP-2 are mediated indirectly through these and/or other intestinal growth factors.

Understanding of GLP-2R signaling to date is primarily based on studies using transfected cell lines that do not express the endogenous GLP-2 receptor [62,77,78,79••], although several recent studies using primary nontransfected cells have provided further insight into GLP-2R signaling [67,68•,69]. Experiments using heterologous baby hamster kidney (BHK) fibroblasts stably transfected with the GLP-2R demonstrate that GLP-2 activates a cAMP-dependent protein kinase A (PKA) pathway [62,77,78,79••]. Similarly, primary rat intestinal mucosal cells [69], rat astrocytes [67], and mouse hippocampal cells [68•] also exhibit increased levels of cAMP in response to GLP-2. In contrast, studies with human colon carcinoma Caco-2 cells suggest that GLP-2 reduces intracellular cAMP content [80,81]; however, neither GLP-2R mRNA nor protein expression has been detected in Caco-2 cells [63,80]. Finally, studies in BHK–GLP-2R cells demonstrate that activation of the GLP-2R increases CRE and AP-1–dependent transcriptional activity [77], whereas GLP-2 increases immediate early c-fos and c-jun gene expression both *in vivo* (rat dorsal medial hypothalamus and mouse enteric ganglia) [64,73] and *in vitro* (BHK–GLP-2R cells and primary rat astrocytes) [67,77]. These changes in early response genes may in part mediate the actions of GLP-2 to increase cell proliferation and survival.

Although the cellular localization of the GLP-2R is suggestive of indirect tropic actions of GLP-2, several *in vitro* studies have suggested that GLP-2 can also directly modulate cell proliferation and survival (Fig. 2). GLP-2 enhanced proliferation in primary rat astrocytes and intestinal mucosal cells [67,69] and in BHK–GLP-2R and Caco-2 cells at pharmacologic concentrations [77,80,82,83]. This GLP-2–stimulated proliferation is

Figure 2. Schematic of the mechanism of action of glucagon-like peptide 2, two possible signaling pathways are activated by the glucagon-like peptide 2 receptor, either direct top or indirect bottom, through yet-to-be-identified endocrine, paracrine and/or neural mediator(s)



dependent on both phosphatidylinositol-3–kinase and mitogen-activated protein kinase (MAPK) pathways in Caco-2 cells [83] but does not involve MAPK signaling in rat mucosal or BHK–GLP-2R cells [69,77]. Furthermore, GLP-2–induced cell proliferation is PKA-dependent in rat mucosal cells but not in BHK–GLP-2R cells [69,77]. Finally, consistent with the growth-promoting effects of GLP-2, GLP-2R activation inhibits cycloheximide-induced apoptosis of BHK–GLP-2R cells in a cAMP-dependent and PKA-independent, MAPK-independent, and phosphatidylinositol-3–kinase—independent manner [78], but decreases glutamate-induced apoptosis of neurons in a PKA-dependent manner [68•]. The antiapoptotic effects of GLP-2 appear to be exerted through a number of different mechanisms, including inhibition of caspase-3, caspase-8, and glycogen synthase kinase 3; inhibition of caspase-dependent cleavage of β-catenin and PKB/Akt; and reduction of mitochondrial association of Bad and Bax and release of cytochrome-C [78,84,85]. More detailed studies of GLP-2 actions on cell growth and survival using nontransformed intestinal cells are needed.

Very recent studies using both BHK–GLP-2R cells and primary rat intestinal mucosal cells have demonstrated that the GLP-2R undergoes homologous desensitization *in vitro* [65,69]. Estall *et al.* [79••] have now demonstrated a novel mechanism underlying the desensitization of this G-protein–coupled receptor that involves lipid rafts in a clathrin-independent and dynamin-independent pathway. Future studies will be necessary to determine whether GLP-2R desensitization is a physiologically relevant phenomenon.

Biologic effects of glucagonlike peptide 2

The primary effect observed after exogenous GLP-2 administration is the stimulation of intestinal mucosal growth, as characterized by an increase in tissue weight and protein and DNA content (Fig. 1) [4,56,58–60, 62,72,86–98]. These effects are independent of changes in food intake and body weight and appear to occur primarily through increased crypt cell proliferation and decreased apoptosis, resulting in enhancement of both villus height and crypt depth [86,87,90]. Furthermore, GLP-2 increases the surface area of the enterocytes [91], which may contribute to the enhanced absorptive capacity seen after GLP-2 administration [92,99]. Consistent with the regional expression of the GLP-2R [62], the tropic effects of GLP-2 are highly specific for the gut [4], with the jejunum demonstrating the greatest response to GLP-2 treatment [86,94,98]. Interestingly, GLP-2 also stimulates intestinal blood flow [100], suggesting that GLP-2–induced gut growth could be mediated, at least in part, through an increase in the delivery of oxygen and essential nutrients. These cumulative growth effects of GLP-2 have been examined in 3-month mouse experiments, in which intestinal growth reaches a plateau and gut weight returns to normal levels 10 days after the end of daily GLP-2 administration [86].

Importantly, the intestinal mass induced by GLP-2 exhibits enhanced digestive and absorptive functional capacity. GLP-2 administered to mice, rats, and both premature and term-delivered neonatal piglets increases brush border digestive enzyme activity [72,92,101,102]. Additionally, GLP-2 treatment has been reported to enhance the absorption of nutrients, including monosaccharides, amino acids, and triglycerides [89,92,97]. Cheeseman's group [103–106] has further reported that GLP-2 enhances the capacity for hexose absorption through increased expression of SGLT-1 in the BBM and increased GLUT-2 activity and insertion into basolateral membrane. These responses represent some of the most rapid effects attributed to GLP-2, occurring with hours of administration.

Complementary to its actions to enhance nutrient digestion and absorption, GLP-2 inhibits antral motility in the pig [107] and inhibits gastric acid secretion in sham-fed humans [108] (collectively known as the *ileal brake* effect). However, two recent studies provide conflicting evidence with respect to the ability of GLP-2 to suppress gastric motility in humans [109•,110•]. Although a number of methodologic factors could explain this discrepancy, the major difference between these studies resides in the nutrient load used to assess gastric emptying (*eg*, 7.5 Kcal of liquid *vs* 310 Kcal of solid food), with the total retention time for the high-calorie meal reported to be at least a magnitude of order greater than that of the low-calorie meal. Thus, the physiologic importance of GLP-2 in mediating the ileal brake effect in humans remains to be established, particularly compared with the greater potency observed with other gastrointestinal hormones such as CCK or the related PGDP, GLP-1 [109•,111].

Consistent with expression of the GLP-2 in the CNS, a study by Tang-Christensen *et al.* [66] demonstrated that GLP-2 can inhibit food intake when injected ICV in rats. However, substantially larger doses of GLP-2 (25–50 μg) are required to produce a similar effect in mice [65]. Furthermore, peripheral injection of GLP-2 in rodents has no effect on food intake and/or weight gain [86,97]. Consistent with the results from the rodent studies, intravenous administration of GLP-2 in humans has no effect on either food intake or appetite/satiety [109•,110•,112]. These findings suggest that GLP-2 produced locally in the brain may function as an anorexigenic neurotransmitter in the central regulation of food intake; however, peripheral GLP-2 does not likely convey an anorectic signal to the brain [113].

Several studies have demonstrated that GLP-2 affects bone homeostasis [99,114,115••,116••]. Initial studies in patients with short bowel syndrome (SBS) demonstrated that treatment with GLP-2 for 5 weeks increases total body bone mass [99] and bone mineral density [114]. Two more recent studies from Henriksen *et al.* [115••,116••] have now demonstrated that subcutaneous injection of GLP-2 acutely decreased serum c-telopeptides of collagen (s-CTX) and urinary deoxypyridindine (u-DPD)/creatinine levels (both markers of bone resorption) but had no effect on bone formation (as measured by s-osteocalcin levels) in fasting postmenopausal women. However, GLP-2 given in the evening to postmenopausal subjects reduced bone resorption and stimulated bone formation [115••]. These beneficial effects of GLP-2 on bone homeostasis are not consequent to enhanced intestinal calcium absorption [114] but, rather, are suggested to be caused by direct or indirect effects on osteoclast and/or osteoblast activity. Consistent with the latter possibility, a recent report has demonstrated the presence of GLP-2R on osteoclasts [117]. Collectively, these findings suggest the novel possibility of a therapeutic role for GLP-2 in the treatment of postmenopausal osteoporosis.

Potential therapeutic roles of glucagon-like peptide 2

Because exogenous GLP-2 administration enhances both growth and differentiated function in the gastrointestinal tract, GLP-2 may be useful for the treatment of a variety of different gastrointestinal disorders. The most advanced human studies of GLP-2 examine the treatment of SBS, which is characterized by severe nutrient malabsorption. In rodent models of SBS, GLP-2 enhances intestinal adaptation through stimulation of mucosal growth, villus height, sucrase activity, and absorptive function [97,118,119]. More recently, GLP-2 administration augmented intestinal adaptation in rats receiving total parenteral nutrition after massive small bowel resection, demonstrating that the permissive effects of GLP-2 during intestinal adaptation are independent of luminal nutrients [95]. Furthermore, in the only study of GLP-2 administration in humans with intestinal insufficiency reported to date, SBS patients without a colon demonstrated increased energy absorption, improved nutrient status, and enhanced bone mass after 5 weeks of treatment with native GLP-2 [99,114]. NPS Pharmaceuticals (Salt Lake City, UT) has now initiated a phase II/III clinical study examining the use of a long-acting GLP-2 analogue, Teduglutide (h[Gly^2]-GLP-2), in patients with SBS (http://www.npsp.com).

Glucagon-like peptide 2 also increases survival and reduces the incidence of mucosal ulceration/damage, inflammation, bacterial translocation, and expression of inflammatory cytokines in experimental models of inflammatory bowel disease and intestinal injury [84,88,120–122]. Furthermore, GLP-2 is effective in reducing intestinal injury and mortality when administered before, in conjunction with, or after induction of inflammation, although GLP-2 administration before injury is most efficacious. Finally, GLP-2 also ameliorates the severity of inflammatory bowel disease in transgenic rats when given either intravenously or intraluminally; however, the intravenous route provides greater efficacy [123]. Teduglutide is now being studied in human subjects with inflammatory bowel disease (http://www.npsp.com).

Chemotherapy often results in severe mucositis, thereby limiting its cumulative administration and therapeutic efficacy in the treatment of human cancers. Studies in rodents have demonstrated that GLP-2 improves survival and reduces mucosal atrophy, apoptosis, and bacterial translocation in experimental chemotherapy-induced mucositis [84,124]. The effects of GLP-2 were most beneficial when administered before chemotherapy. Treatment of mice with metformin and a dipeptidylpeptidase IV inhibitor also reduced the deleterious effects of chemotherapy in mice and suggested a relation between

increased plasma levels of GLP-2 and mucosal protection [125]. Importantly, GLP-2 treatment of tumor-bearing rats and mice was found to have no effect on tumor growth [84,94]. Nonetheless, Thulesen *et al.* [126••] reported that GLP-2 has a permissive effect on the growth of 1,2-dimethylhydrazine–induced colonic polyps and adenomas in mice. Furthermore, GLP-2R expression was detected in a small minority of human intestinal carcinoid tumors [63]. Thus, additional studies examining whether GLP-2 promotes growth of human intestinal tumors appear prudent.

Conclusion

A number of exciting studies over the past year have expanded understanding of the intestinotropic actions of GLP-2. In addition, several novel targets for GLP-2 action have been elucidated, with the most notable being the osteoclast, and the need for additional data on the effects of GLP-2 in human subjects with intestinal disease has assumed increasing importance. Much remains to be learned about the biology of GLP-2 action, starting with the exact cellular targets and mechanisms transducing GLP-2 action in the intestine. Given the potential use of GLP-2 analogues for the treatment of human disease, much more work needs to be done to understand the therapeutic potential and mechanisms of action of GLP-2 *in vivo*.

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