Invited mini review

New frontiers in the biology of GLP-2

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Abstract

Glucagon-like peptide-2 (GLP-2) is a 33 amino acid peptide hormone released from the intestinal endocrine cells following nutrient ingestion. GLP-2 exerts trophic effects on the small and large bowel epithelium via stimulation of cell proliferation and inhibition of apoptosis. GLP-2 also upregulates intestinal glucose transporter activity, and reduces gastric emptying and gastric acid secretion. The activity of GLP-2 is regulated in part via renal clearance and cleavage by the aminopeptidase dipeptidyl peptidase IV. In experimental models of intestinal disease, GLP-2 reversed parenteral nutrition-induced mucosal atrophy and accelerated the process of endogenous intestinal adaptation in rats following major small bowel resection. GLP-2 also markedly attenuated intestinal injury and weight loss in mice with chemically-induced colitis, and significantly reduced mortality, bacterial infection and intestinal mucosal damage in mice with indomethacin-induced enteritis. The actions of GLP-2 are transduced by a recently cloned glucagon-like peptide-2 receptor (GLP-2R) that represents a new member of the G protein-coupled receptor superfamily. The GLP-2R is expressed in a highly tissue-specific manner predominantly in the gastrointestinal tract and GLP-2R activation is coupled to increased adenylate cyclase activity. The available evidence suggests that the biological properties of GLP-2 merit careful therapeutic assessment in selected human diseases characterized by injury and defective repair of the gastrointestinal epithelium. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

Tissue-specific processing of proglucagon results in the synthesis of several biologically relevant peptides (Fig. 1). Glucagon, glucagon-like peptide-1 (GLP-1) and glucagon-like peptide-2 (GLP-2), all of which are derived from proglucagon, are highly homologous and have been implicated in regulating many metabolic pathways and physiological systems [1]. Glucagon, secreted by the pancreatic A-cells in the islets of Langerhans, is a well established regulator of glucose metabolism [1–3]. Following the elucidation of the structure and sequence of the proglucagon cDNAs and genes, two glucagon-related peptides, GLP-1 and GLP-2, were found carboxyterminal to the glucagon sequence in proglucagon (Fig. 1). A substantial body of experimental evidence implicates GLP-1 as a

multipotential regulator of blood glucose via effects on appetite, gastric emptying and both insulin and glucagon secretion [1,4]. In contrast, until very recently, the biological actions of GLP-2 have remained unknown. The aim of this manuscript is to review the key studies that have elucidated the biological relevance and mechanism of action of GLP-2.

GLP-2 is an intestinotrophic hormone that promotes expansion of the epithelial mucosa through stimulation of crypt cell proliferation and the inhibition of cell death in the intestinal epithelium [4–6]. A potential link between increased secretion of the glucacon-related peptides and the development of intestinal villus hyperplasia was first established following clinical reports of patients with glucagon-secreting tumors who presented with small bowel villus hyperplasia [5,6]. These cases stimulated considerable interest in the relationship between increased secretion of intestinal glucagon-related peptides and the response to intestinal injury in both rodents and in human subjects with intestinal disease [7–9].

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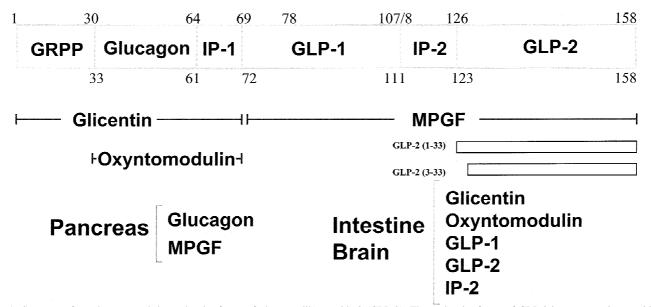# Structural Organization of Mammalian Preproglucagon

Fig. 1. Structure of proglucagon and the molecular forms of glucagon-like peptide-2 (GLP-2). The molecular forms of GLP-2-immunoreactive peptides include the major proglucagon fragment (MPGF), bioactive GLP-2$^{1-33}$ and the bioinactive GLP-2$^{3-33}$.

Despite an extensive series of experiments linking increased proglucagon gene expression and increased secretion of the intestinal proglucagon-derived peptides (PGDPs) with experimental intestinal injury [10–16], the identity of the specific PGDP with intestinotrophic activity proved elusive. Following the observation that mice harboring subcutaneous glucagonomas exhibited significant villus hyperplasia of the small bowel epithelium, peptide injection experiments identified GLP-2 as the PGDP with significant intestinotrophic activity in vivo [17].

2. GLP-2 synthesis and secretion

GLP-2 and GLP-1 are generated via post-translational processing of proglucagon [18,19] and are liberated in enteroendocrine L-cells as a consequence of the expression of a specific profile of prohormone convertase enzymes [20]. GLP-2 is also synthesized in the brainstem and hypothalamus [21,22] of the central nervous system (CNS) although the factors regulating CNS GLP-2 synthesis and release are less well understood.

At least three molecular forms (Fig. 1) of GLP-2 have been identified [23] consisting of bioactive GLP-2$^{1-33}$ and two inactive forms, GLP-2$^{3-33}$ and the major proglucagon fragment (MPGF). Determinants of GLP-2 metabolism include renal clearance [24] and enzymatic inactivation by dipeptidyl peptidase IV (DP IV) at the penultimate amino acid residue rendering GLP-2 biologically inactive [23,25]. The finding that GLP-2 is rapidly inactivated by cleavage at the position-2 alanine has stimulated the development of

DP IV-resistant GLP-2 analogues such as [Gly2]-GLP-2 that exhibit increased potency in vivo [25,26].

Consistent with numerous studies demonstrating nutrient-dependent increases in intestinal GLP-1 secretion [1,4], GLP-2 is also secreted following nutrient challenge in vivo [23,27]. Analysis of GLP-2 secretion in human feeding studies demonstrated that the control of meal-stimulated GLP-2 release is sensitive to nutrient composition [28]. Isocaloric meals enriched in carbohydrates or fats potentate GLP-2$^{1-33}$ secretion 2–5 fold over basal levels, whereas isocaloric meals consisting of protein did not stimulate post-prandial GLP-2$^{1-33}$ release. Meal-stimulated GLP-2$^{1-33}$ release is biphasic, with an early peak occurring 10-min post-ingestion and a second peak detectable about 1 h later depending on meal size [28,29]. This biphasic response is consistent with a rapid initial humoral or neural phase of PGDP release likely under vagal control [30,31] followed by a later phase possibly attributable to a direct interaction between undigested luminal contents and the distally located intestinal L-cells or through physical forces arising via fluctuations in ileal volumes [29].

Several lines of experimental evidence suggest that mild to moderate intestinal injury in animal studies is associated with increased circulating levels of the intestinal PGDPs including GLP-2 [8,16,32,33]. Similarly, human subjects with inflammatory bowel disease (IBD) exhibit increased levels of plasma GLP-2, and a relative shift in the ratio of GLP-2$^{1-33}$:GLP-2$^{3-33}$, resulting in increased levels of bioactive GLP-2$^{1-33}$ in IBD patients [34]. In contrast, more severe damage to the intestinal mucosa, as observed in mice with severe colitis, likely results in destruction of GLP-2-secreting enteroendocrine cells and reduced capaci-

ty for GLP-2 biosynthesis [35]. Furthermore, resection of large amounts of functional intestinal mucosa, as occurs in human subjects with short bowel syndrome, results in lower levels of fasting GLP-2 and deficiencies in meal-stimulated GLP-2 release [29].

3. Physiology of GLP-2 action

The earliest description of GLP-2 bioactivity was the stimulation of small bowel mucosal hyperplasia in GLP-2-treated mice [17]. The expansion of the villus epithelium is attributable to increased crypt cell proliferation and decreased enterocyte apoptosis [36]. The intestinotrophic properties of GLP-2 were subsequently confirmed in several independent studies [37–39]. Although the small bowel is most sensitive to the trophic actions of GLP-2, a modest increment increase in the mass of the colonic epithelium is also observed following treatment with more potent GLP-2 analogues [26].

Although GLP-2 hypersecretion from glucagonomas induces bowel growth [17], few models exist where endogenous GLP-2 hypersecretion is associated with hyperplasia of the mucosal epithelium. A notable exception appears to be experimental rodent diabetes, where increased secretion of intestinal PGDPs leads to elevated levels of circulating GLP-2 and increased mucosal thickness in the small bowel [40,41]. Treatment of diabetic rats with insulin lowers the levels of circulating GLP-2 and reverses the mucosal hyperplasia in the small bowel [41].

Following treatment of mice and rats with exogenous GLP-2 for 7–10 days, a marked increase in villus height and small bowel mass and a smaller increment in small bowel length is consistently observed [17,25,26,36,42]. The GLP-2-treated bowel exhibits normal protein and RNA content, and comparable levels of intestinal enzymes such as maltase, sucrase, lactase, glutamyl transpeptidase and DP IV following normalization for bowel weight [43]. Furthermore, nutrient absorption is normal to enhanced in mice treated with GLP-2 for 10 days. Consistent with these findings, GLP-2 infusion in TPN-fed rats upregulates the expression of digestive enzyme gene expression [44]. In contrast to GLP-1, acute administration of GLP-2 has no effect on oral glucose tolerance [43]. These findings demonstrate that the morphological macromolecular changes in the small bowel epithelium that accompany GLP-2 treatment are likely to be associated with normal to enhanced intestinal absorptive function in vivo.

In addition to the intestinotrophic effects of GLP-2 that require several days of GLP-2 administration to become evident, several more rapid actions of GLP-2 have been described that are detectable within minutes following intravenous GLP-2 infusion. These include stimulation of hexose transport and induction of glucose transporter activity in the rat small bowel epithelium, and inhibition of insulin-stimulated antral motility in the pig [45]. GLP-2 infusion also reduced sham feeding-stimulated gastric acid secretion in healthy human subjects, albeit at high to supraphysiological levels of plasma GLP-2 [46]. Although GLP-2 stimulates adenylate cyclase activity in hypothalamic and pituitary extracts in vitro [47], the role of GLP-2 in the CNS in vivo remains unclear.

4. Therapeutic application of GLP-2 in experimental intestinal injury

The observation that GLP-2 promotes expansion of the intestinal epithelium has stimulated considerable interest in the potential therapeutic role of GLP-2 in the setting of intestinal disease. Given the demonstrated importance of enteral nutrition in both the maintenance of the intestinal epithelial mucosa and the stimulation of GLP-2 secretion, Chance and colleagues examined the trophic effects of GLP-2 in parenterally fed rats. Remarkably, whereas rats maintained only on intravenous nutrition exhibited marked mucosal atrophy, co-infusion of GLP-2 along with parenteral nutrition completely reversed villus atrophy and mucosal hypoplasia in the small bowel [48].

As major small bowel resection is associated with increased secretion of the intestinal PGDPs and increased proglucagon gene expression in the intestinal remnant [14,15], a role for GLP-2 in intestinal adaptation seems plausible. Rats subjected to major small bowel resection (MSBR) exhibit an endogenous adaptive response that is significantly augmented, predominantly in the jejunum, by concomitant treatment with h[Gly2]-GLP-2 [49]. In addition to upregulation of DNA, RNA and protein synthesis, a significant reduction in xylose absorption observed in control resected rats was completely reversed in resected rats receiving h[Gly2]-GLP-2. These findings, taken together with the observation that human patients with short bowel syndrome exhibit defective GLP-2 secretion in response to nutrient challenge, suggest that GLP-2 replacement in patients with short bowel syndrome merits further evaluation [29].

The therapeutic potential of GLP-2 has also been tested in rodents with intestinal injury and inflammatory bowel disease. Mice with dextran sulfate-induced colitis exhibit severe intestinal injury and weight loss that is markedly attenuated following twice daily co-administration of h[Gly2]-GLP-2 [35]. Similarly, small bowel injury that rapidly ensues following induction of enteritis with indomethacin treatment is significantly improved by the administration of h[Gly2]-GLP-2 [50]. Remarkably, administration of GLP-2 prior to, concomitant with or following indomethacin administration significantly improved survival in mice. Furthermore, GLP-2 improved histological indices of disease activity and markedly reduced the prevalence of bacterial infection [50].

Positive effects of GLP-2 treatment have also been observed following ischemic bowel injury in rats. Intraven-

ous infusion of GLP-2 following superior mesenteric artery occlusion enhanced mucosal repair and significantly decreased mortality [51]. Taken together, the available evidence clearly demonstrates that GLP-2 exhibits utility in preventing bowel injury, and in enhancing the reparative response to intestinal injury in both the small and large bowel.

5. GLP-2 action and the GLP-2 receptor

The mechanisms by which GLP-2 rapidly enhances intestinal glucose transport within minutes of administration remain poorly understood. An important advance in the study of GLP-2 action was the cloning of the human and rat GLP-2 receptors [52] by Munroe and colleagues at Corp. Allelix. The mammalian GLP-2 receptor shares considerable sequence identity with the glucagon and GLP-1 receptors and with related members of the glucagon-secretin receptor superfamily [52]. Analysis of GLP-2 receptor expression by RNAse protection and RT-PCR, detected GLP-2R mRNA in rodent stomach, intestine and brain [52]. Accordingly, in contrast to the more widespread expression patterns of the glucagon and GLP-1 receptors [53–55], the expression of the GLP-2 receptor is restricted to a much smaller number of tissues. The available evidence suggests that many of the actions of GLP-2 may be indirect, via liberation of downstream effectors of GLP-2 action.

Consistent with findings in studies of glucagon and GLP-1 signaling [1], GLP-2 stimulates increased adenylate cyclase activity in fibroblasts transfected with the GLP-2 receptor [52,56]. Activation of AP-1-dependent signaling pathways, as exemplified by induction of transcriptional activity of reporter genes containing AP-1 responsive elements, is also observed following GLP-2 stimulation [56], although these actions of GLP-2 are likely indirect and mediated by the protein kinase A-dependent pathway. In contrast to studies demonstrating activation of calcium influx by either glucagon or GLP-1, we did not detect changes in intracellular calcium following activation of the GLP-2 receptor in BHK fibroblasts. A modest stimulation of fibroblast proliferation and immediate early gene expression was observed using nanomolar concentrations of GLP-2 in vitro [56], however, whether physiological levels of GLP-2 directly stimulates intestinal epithelial proliferation has not yet been determined.

6. GLP-2: summary and future research directions

The identification of several biological activities for GLP-2 significantly expands the pleiotropic activities ascribed to the peptides encoded by the proglucagon gene. Although we have learned a great deal over the past 4 years, many important questions remain unanswered. For example, the cellular localization and signaling properties of the endogenous intestinal GLP-2 receptor have not yet been described. Whether the trophic and metabolic activities of GLP-2 in the intestine represent essential or redundant biological actions awaits the development of potent and specific GLP-2 antagonists and/or a GLP-2 receptor knockout mouse. What are the actions, if any, of GLP-2 in the CNS? Given the substantial evidence supporting beneficial effects of GLP-2 in preclinical experimental models of intestinal injury, does GLP-2 have a role in the treatment of human intestinal diseases characterized by epithelial damage or suboptimal nutrient absorption? If we have learned anything from the track records of glucagon and GLP-1 research, it seems likely that the study of GLP-2 action will likely prove to be an exciting and fruitful area with potential clinical relevance for the treatment of several human intestinal diseases characterized by defective repair or function of the intestinal mucosa.

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