Glucagon-like peptide-2: New insights, new questions

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ARTICLES

Yusta B, Huang L, Monroe D, Wolff G, Fantiske R, Charma S, Demchysyn L, Asa S, Drucker DJ. Enteroendocrine localization of GLP-2 receptor expression in humans and rodents. *Gastroenterology* 2000;119:744-55.

Benjamin MA, McKay DM, Yang P-C, Cameron H, Perdue MH. Glucagon-like peptide-2 enhances intestinal epithelial barrier function of both transcellular and paracellular pathways in the mouse. *Gut* 2000;47:112-9.

The actions of glucagon-like peptide-2 (GLP-2) occur through binding to a single G protein-coupled GLP-2 receptor (GLP-2R); however, the cell types expressing this receptor in the gastrointestinal tract are unknown. In the study of Yusta et al, GLP-2R expression in rodent and human tissues was examined using a combination of reverse-transcription polymerase chain reaction (RT-PCR), Northern blotting and immunocytochemistry. A single major GLP-2 mRNA transcript of approximately 5.8 kb was detected in rodent stomach, duodenum, jejunum, ileum and colon, but not esophagus. Levels of expression were relatively higher in the small and large bowel. GLP-2R expression was also detected by RT-PCR in RNA from the hypothalamus, brain stem and lung. Using a specific GLP-2R antisera, GLP-2R immunoreactive cells were identified in the human antrum, at the base of the small intestinal villus

epithelium, along the length of the crypt-villus axis and in the colon. These cells also showed chromogranin and serotonin immunopositivity, suggesting that the source was endocrine cells. The endocrine cell types containing GLP-2R also contained peptide tyrosine tyrosine (PYY), GLP-1 and occasionally gastric inhibitory peptide (GIP). No somatostatin or cholecystokinin cells were GLP-2R immunopositive. GLP-2R immunoreactivity was not detected in nonendocrine gastrointestinal cells, and GLP-2R mRNA transcripts were not detected in any of several intestinal or endocrine cell lines examined. The results show that, in contrast to glucagon and GLP-1, GLP-2 receptors are in relatively low abundance in the gastrointestinal tract and are specifically localized to endocrine cells. The findings suggest that the actions of GLP-2 on growth, intestinal motility and gastric acid secretion are indirect and are facilitated by one or more unknown downstream mediators.

Alterations in epithelial permeability occur in several disorders of the gastrointestinal tract and may be a primary defect predisposing patients to Crohn's disease. Several factors increase epithelial permeability (eg, bacterial toxins, cytokines), while others, notably growth factors (eg, transforming growth factor-beta, epidermal growth factor) restore mucosal integrity. The study by Benjamin et al sought to determine whether GLP-2, a peptide with relatively specific growth effects on intestinal mucosa, regulates intestinal epithelial barrier function. Synthetic GLP-2 or a synthetic protease-resistant GLP-2 analogue h[Gly²] GLP-2, given subcutaneously at a dose of 5 µg, or normal saline was administered to mice twice daily for 10 days. Jejunal segments were mounted in Ussing chambers, and tissue conductance and unidirectional fluxes were determined for

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sodium ions, chromium EDTA (a small 360 kDa lipid-insoluble molecule that assesses paracellular permeability) and horseradish peroxidase (which traverses the epithelium by transcytosis and allows quantification of transepithelial transport). Similar results were obtained with both preparations of GLP-2, although more potent effects occurred with the protease-resistant analogue. Intestinal wet weight increased 140%, villus height increased 40% and the villus to crypt ratio increased from 5.1 to 7.2 compared with that of controls, thus confirming the role of GLP-2 as a regulator of intestinal growth. Serosal to mucosal flux of sodium ions and chromium EDTA were each reduced by 35%, whereas the flux of horseradish peroxidase was reduced by 80% after 10 days of treatment. Similar effects on permeability occurred after 4 h of treatment with GLP-2, before any morphological alterations. Thus, GLP-2 administered to mice directly enhances barrier function of intestinal epithelium by influencing both paracellular and transcellular pathways, independent of any morphological changes.

COMMENT

The intestinal proglucagon-derived peptides secreted from endocrine cells of the small and large intestine are now known to be comprised of glicentin, oxyntomodulin, GLP-1 and GLP-2. The physiological roles of glicentin and oxyntomodulin continue to be elucidated. However, it is now recognized that GLP-1 has a wide spectrum of biological effects including regulation of gastric emptying and gastric acid secretion, appetite control and most notably stimulation of glucose-dependent insulin secretion, suggesting a possible treatment for non-insulin dependent diabetes. Thirty years ago, Gleeson et al (1) described a patient with an enteroglucagon-secreting endocrine tumour in the kidney that was associated with marked intestinal hyperplasia. More recently, an elegant series of studies by Drucker and colleagues (2-4) identified GLP-2 as a potent and specific stimulator of small intestinal growth. These findings led to studies showing that GLP-2 prevents the mucosal hypoplasia associated with total parenteral nutrition in rats and facilitates intestinal adaptation with improved nutrient absorption and nutritional status in the short bowel syndrome in rats (5) and humans (6). GLP-2 also has been shown to improve the intestinal damage observed in exper-

imental models of ischemia and inflammation (7). The study by Yusta et al provided further insight into GLP-2 physiology, with the rather surprising finding that the GLP-2 receptor is localized to a minority of endocrine cells in the gut. These results imply that the intestinal trophic effects of GLP-2 are likely indirect and mediated by as yet unidentified growth factor(s) or peptide(s), the actions of which also must be relatively specific to the gut. Conceivably, different factors acting either by conventional endocrine or by paracrine mechanisms may preferentially mediate the intestinal effects of GLP-2 on motility, growth and intestinal epithelial barrier function. Some support for this notion came from the studies of Benjamin et al, who demonstrated that GLP-2 improves epithelial barrier function both via paracellular and transcellular pathways, independent of any morphological changes. Because disruption of the epithelial barrier with antigen uptake may contribute to the intestinal damage associated with inflammatory bowel disease, the beneficial effects of GLP-2 in mouse models of colitis may, therefore, in part, be related to improved barrier function. Together, these two studies provide important contributions to the understanding of GLP-2 physiology and provide the impetus for considering a potential role of GLP-2 in the management of patients with compromised gut function due to either resection or inflammation.

REFERENCES

1. Gleeson MH, Bloom SR, Polak JM, Henry K, Dowling RH. Endocrine tumour in kidney affecting small bowel structure, motility, and absorptive function. *Gut* 1971;12:773-82.
2. Drucker DJ, Erlich P, Asa SL, Brubaker PL. Induction of intestinal epithelial proliferation by glucagon-like peptide 2. *Proc Natl Acad Sci USA* 1996;93:7911-16.
3. Drucker DJ, Shi Q, Crivici A, et al. Regulation of the biological activity of glucagon-like peptide 2 in vivo by dipeptidyl peptidase IV. *Nat Biotechnol* 1997;15:673-77.
4. Munroe DG, Gupta AK, Kooshesh F, et al. Prototypic G protein-coupled receptor for the intestinotrophic factor glucagon-like peptide 2. *Proc Natl Acad Sci USA* 1999;96:1569-73.
5. Scott RB, Kirk D, MacNaughton WK, Meddings JB. GLP-2 augments the adaptive response to massive intestinal resection in rat. *Am J Physiol* 1998;275:G911-21.
6. Jeppesen PB, Hartmann B, Thulesen J, et al. Glucagon-like peptide 2 improves nutrient absorption and nutritional status in short-bowel patients with no colon. *Gastroenterology* 2001;120:806-15.
7. Drucker DJ, Yusta B, Boushey RP, DeForest L, Brubaker PL. Human [Gly2]GLP-2 reduces the severity of colonic injury in a murine model of experimental colitis. *Am J Physiol* 1999;276:G79-91.