Digestive Diseases and Sciences (2020) 65:3422–3424
https://doi.org/10.1007/s10620-020-06303-5

EDITORIAL

Why Recycling Matters: Glucagon-Like Peptide-2 and the Regulation of Intestinal Sodium and Fluid Absorption

Patricia L. Brubaker[1,2]

Published online: 30 April 2020

Short bowel syndrome (SBS) with intestinal failure represents a life-altering condition, with many patients dependent upon partial or total parenteral nutrition (TPN) for survival. In the absence of pharmacological therapies directed at improving intestinal growth and function, the recent development of a degradation-resistant analog of the gut hormone glucagon-like peptide-2 (GLP-2), teduglutide (human (h) Gly^2-GLP-2^{1-33}), has represented a lifeline for many of these patients, reducing and even eliminating the need for parenteral nutrition. Nevertheless, although the mechanisms underlying the intestinal growth effects of GLP-2 have been subject to intense study, those mediating the pro-absorptive actions of this peptide are less well understood.

Following the seminal observation in 1996 that the native intestinal hormone GLP-2^{1-33} enhances intestinal growth in normal mice [1], many studies demonstrated similar effectiveness of GLP-2 in models of intestinal resection and disease, as well as in humans with SBS (reviewed in [2]). Yet, although the possibility of GLP-2-related enhancement of intestinal barrier function was first suggested by Chance et al. [3], it was not until the pioneering studies of Benjamin et al. [4] that both GLP-2 and hGly^2-GLP-2^{1-33} were convincingly demonstrated to reduce intestinal paracellular permeability to ions (pore pathway; i.e., Na^+) as well as to small organic solutes (leak pathway; i.e., Cr-EDTA) and large proteins (transcellular/transcytosis pathway; i.e., horseradish peroxidase) in normal mice (Fig. 1). In animal models of intestinal disease, GLP-2 was also reported to be of benefit in chemotherapy-induced enteritis through decreasing bacterial translocation [5]. Furthermore, several studies have now shown that the barrier-strengthening actions of GLP-2 with respect to both ion flux and several organic solutes such as fluorescein isothiocyanate-$dextran^{4kDa}$ are mediated, at least in part, though increased expression and/or improved subcellular localization of proteins that constitute the key barrier-forming tight junctional complex between the intestinal epithelial cells, in both healthy mice and murine models of disease [6, 7]. In more recent studies, treatment with GLP-2 also reduced intestinal permeability to several other small solutes (i.e., mannitol and polyethylene glycol 380–420) in a neonatal piglet model of SBS [8]. Since a beneficial effect of teduglutide is related to increased fluid and ion absorption in patients with SBS [9], the recent study by Reiner et al. [10] now offers insight as to how these apparently conflicting findings may be resolved.

Using a murine model of SBS with intestinal failure, Reiner et al. [10] demonstrated that not only did teduglutide treatment stimulate intestinal growth and improve survival, but it also reduced the water content of stools and lowered plasma aldosterone concentrations, consistent with improved fluid and electrolyte absorption. The changes also correlated, albeit in a limited fashion, with expression as well as translocation of the renal electrogenic epithelial sodium channel (ENaC) away from the collecting duct cell membrane, in keeping with the mechanism of action of aldosterone and consistent with improved Na^+ balance. Nonetheless, while teduglutide treatment decreased intestinal permeability to a probe of the paracellular leak pathway, fluorescein isothiocyanate-$dextran^{4kDa}$, as expected, it also normalized cation size selectivity mediated through the tight junctional pore pathway. When taken with a lack of effect on fecal Na^+ content, these findings suggested that teduglutide may enhance intestinal Na^+ recirculation though active Na^+ uptake via the intestinal Na^+: glucose cotransporter SGLT1 [as reviewed in [2]] in combination with actions on the paracellular pore pathway by which submucosal Na^+ diffuses through tight junctions down its concentration gradient to

✉ Patricia L. Brubaker
p.brubaker@utoronto.ca

[1] Department of Physiology, University of Toronto, Rm 3366, Medical Sciences Building, 1 King's College Circle, Toronto, ON M5S 1A8, Canada

[2] Department of Medicine, University of Toronto, Rm 3366, Medical Sciences Building, 1 King's College Circle, Toronto, ON M5S 1A8, Canada

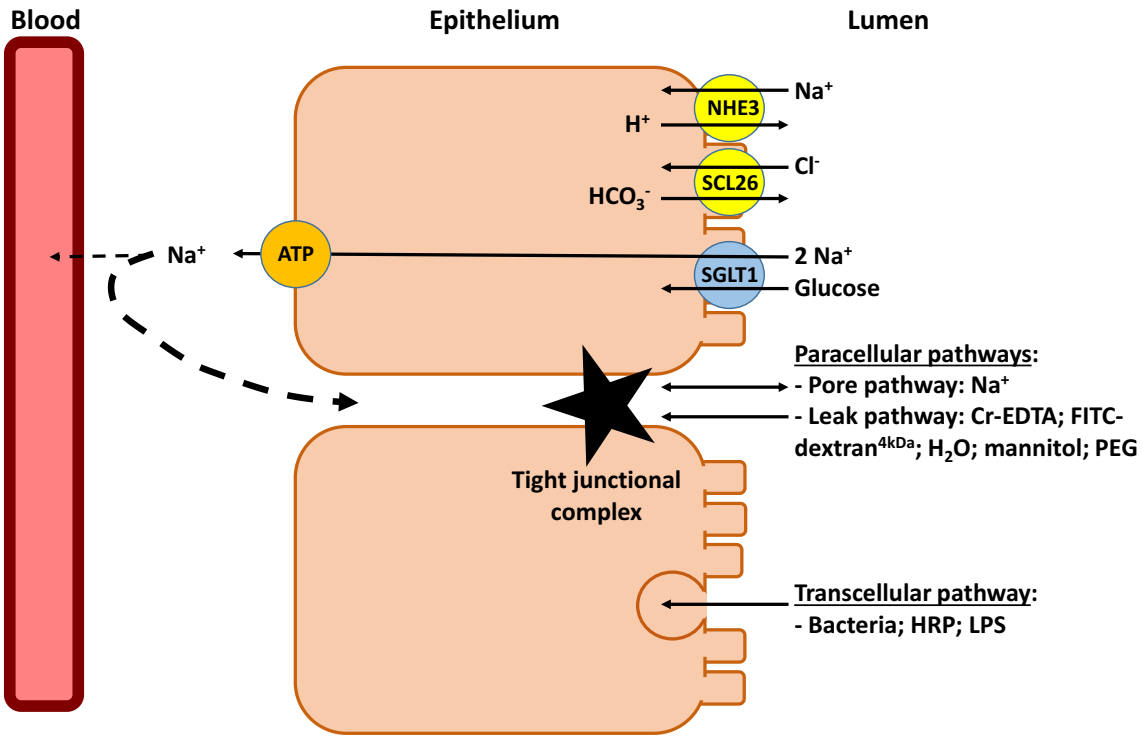

Fig. 1 Overview of small intestinal absorption of select ions, small and large molecules, and bacteria, through different transporters and pathways. The thickness of the dashed lines indicates the extent of the contribution to Na^+ flux. *FITC* fluorescein isothiocyanate, *HRP* horseradish peroxidase, *NHE3* sodium-hydrogen antiporter, *PEG* polyethyleneglycol 380-420, *SLC26* anion solute carrier 26, *SGLT1* sodium-glucose luminal transporter 1

the lumen (Fig. 1). More mechanistically, changes in transcript expression of tight junction proteins were limited to increases in claudin-10, which contributes to paracellular ion permeability in the crypts. Furthermore, immunoreactive levels of claudin-10 protein were unexpectedly increased in the villus tips where the Na^+-dependent glucose transporter SGLT-1 is also localized. Finally, given that numerous studies demonstrate that the actions of GLP-2 on the intestinal epithelium are indirect, mediated through a number of secondary signaling molecules (i.e., epidermal growth factor, insulin-like growth factor-1, keratinocyte growth factor, nitric oxide synthase, vasoactive intestinal polypeptide, etc.; reviewed in [2]), Reiner et al. [10] also showed that the changes in fluid balance were largely independent of NOD2 (nucleotide-binding, oligomerization domain-containing protein 2), which has been implicated as a risk factor for intestinal failure.

When taken together, the findings of Reiner et al. [10] suggest that teduglutide treatment not only promotes intestinal growth, but also facilitates Na^+ recirculation, considered the primary mechanism by which many nutrients such as sugars and amino acids are absorbed, through alterations in claudin-10, in a murine model of SBS with intestinal failure. Although the findings may help to resolve the apparent paradox of teduglutide-induced decreases in paracellular permeability and increases in nutrient, Na^+ and fluid absorption, many questions remain. For example, given that Benjamin et al. [4] demonstrated that GLP-2 reduces paracellular Na^+ permeability in normal mice, are the current results specific to the murine SBS model of intestinal failure? Can the findings be reproduced in other models of intestinal damage or disease, and/or to other species, suggesting that they may be translatable to the clinic? Also, as studies in both healthy rodents and disease models have reported effects of GLP-2 on multiple intestinal tight junction proteins, including occludin, zona occludens (ZO)-1 and claudin-3 and claudin-7 [6, 7], it will be necessary to determine the essential contribution of claudin-10 toward fluid homeostasis using a knockout approach. Furthermore, the current study is limited in its analysis of male mice only, as well as in its conclusion that NOD2 is not a mediator of GLP-2 actions, given its use of C57Bl/6J mice rather than littermate controls derived from breeding of NOD2 heterozygous animals (i.e., due to the possible impact of differential intestinal microbiomes). Finally, as GLP-2 requires other mediators for its effects on the intestine, which molecule is directly responsible for the changes in fluid absorption if not related to NOD2 signaling? These questions notwithstanding the findings provide novel insight into at least one possible mechanism by which teduglutide treatment enhances the absorption of both luminal

fluids and nutrients in patients with SBS-associated intestinal failure.

Funding P.L. Brubaker is supported by the Canada Research Chairs program. Studies on GLP-2 in the Brubaker laboratory are funded by an operating grant from the Canadian Institutes of Health Research (PJT-14853).

Compliance with Ethical Standards

Conflict of interest The author has no relevant conflicts of interest to disclose.

References

1. Drucker DJ, Erlich P, Asa SL, et al. Induction of intestinal epithelial proliferation by glucagon-like peptide 2. *Proc Natl Acad Sci USA*. 1996;93:7911–7916.
2. Brubaker PL. Glucagon-like peptide-2 and the regulation of intestinal growth and function. *Compr Physiol*. 2018;8:1185–1210.
3. Chance WT, Foley-Nelson T, Thomas I, et al. Prevention of parenteral nutrition-induced gut hypoplasia by coinfusion of glucagon-like peptide-2. *Am J Physiol*. 1997;273:G559–G563.
4. Benjamin MA, McKay DM, Yang PC, et al. Glucagon-like peptide-2 enhances intestinal epithelial barrier function of both transcellular and paracellular pathways in the mouse. *Gut*. 2000;47:112–119.
5. Boushey RP, Yusta B, 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*. 2001;61:687–693.
6. Cani PD, Possemiers S, Van de Wiele T, et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut*. 2009;58:1091–1103.
7. Dong CX, Zhao W, Solomon C, et al. The intestinal epithelial insulin-like growth factor-1 receptor links glucagon-like peptide-2 action to gut barrier function. *Endocrinology*. 2014;155:370–379.
8. Lim DW, Levesque CL, Vine DF, et al. Synergy of glucagon-like peptide-2 and epidermal growth factor coadministration on intestinal adaptation in neonatal piglets with short bowel syndrome. *Am J Physiol Gastrointest Liver Physiol.*. 2017;312:G390–G404.
9. Iyer KR, Kunecki M, Boullata JI, et al. Independence from parenteral nutrition and intravenous fluid support during treatment with teduglutide among patients with intestinal failure associated with short bowel syndrome. *J Parenter Enteral Nutr.*. 2017;41:946–951.
10. Reiner J, Berlin P, Wobar J, et al. Teduglutide promotes epithelial tight junction pore function in murine short bowel syndrome to alleviate intestinal insufficiency. *Dig Dis Sci*. (Epub ahead of print). https://doi.org/10.1007/s10620-020-06140-6.