Title
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Journal
Current Opinion in Gastroenterology, 31(6)

ISSN
0267-1379

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Publication Date
2015-11-01

DOI
10.1097/mog.0000000000000211

Peer reviewed

HHS Public Access

Author manuscript

Curr Opin Gastroenterol. Author manuscript; available in PMC 2016 November 01.

Published in final edited form as:

Curr Opin Gastroenterol. 2015 November ; 31(6): 486–491. doi:10.1097/MOG.0000000000000211.

Gastroduodenal Mucosal Defense Mechanisms

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Abstract

Purpose of Review—To highlight recent developments in the field of gastroduodenal mucosal defense with emphasis on lumen-gut interactions.

Recent Findings—There has been a growing interest in the physiological functions of luminal chemosensors present from tongue to colon that detect organic molecules in the luminal content associated with nutrient ingestion, usually associated with specialized cells, in particular the enteroendocrine cells. These receptors transduce the release of peptide hormones, in particular proglucagon-derived products such as the glucagon-like-peptides (GLPs), which have profound effects on gut function and on metabolism. Luminal chemosensors transduce GLP release in response to changes in the cellular environment, as part of the mechanism of nutrient chemosensing. GLP-2 has important trophic effects on the intestinal mucosa, including increasing the proliferation rate of stem cells and reducing transmucosal permeability to ions and small molecules, in addition to increasing the rate of duodenal bicarbonate secretion. GLP-1, although traditionally considered an incretin that enhances the effect of insulin on peripheral tissues, also has trophic effects on the intestinal epithelium.

Summary—A better understanding of the mechanisms that mediate GLP release can further illuminate the importance of nutrient chemosensing as an important component of the mechanism that mediates the trophic effects of luminal nutrients. GLP-1 and -2 are already in clinical use for the treatment of diabetes and intestinal failure. Improved understanding of the control of their release and their end-organ effects will identify new clinical indications and interventions that enhance their release.

Keywords

Glucagon-like-peptides; gut taste receptors; free fatty acid receptors; trophic feeds; nutrient chemosensing; gastric mucosal defense

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Conflicts of interest

None

Introduction

The decades-old observation that the gut atrophies during starvation serves as the basis for the concept of “trophic feeds” in which small amounts of luminal nutrients prevent mucosal atrophy, even when the overall nutritional status is inadequate. The mechanism on which this concept is based has usually been attributed to dietary components such as glutamine, which serve as direct “fuels” for enterocytes, based largely on in vitro studies [1]. Nevertheless, numerous observations support an alternative concept, in which trophic effects of luminal molecules are mediated mostly by hormonal mechanisms. Our overall theme will be to highlight some of the recent publications that support this hypothesis.

An important, early, and yet mostly unheralded observation supporting this hypothesis was published in 1958 by Flatt *et al.* [2], in which the addition of exogenous short-chain fatty acids (SCFAs) to the rumen of calves was observed to be trophic to the rumen mucosa. Since SCFAs are biologically produced by the oral microflora, an acute load of SCFAs alone may be enough to stimulate a physiological response, thus implicating external SCFA trophic feeds as possible therapies for intestinal damage. This type of experiment has been repeated in numerous models, in particularly the piglet model, in which the trophic effects of SCFAs occurred in intestinal segments remote to the one exposed, suggesting that the trophic effects of SCFAs is not due to direct mucosal exposure[3]. This effect supported the concept that indigestible dietary fibers, which comprise most of the ruminant diet, generate microbial fermentation products that are trophic to the mucosa [4,5]. Despite data such as those just cited, to the contrary, the prevailing hypothesis regarding the trophic effects of luminal SCFAs usually centers on the SCFA butyrate acting as a direct energy source for colonocytes [6*]. Indeed, cultured absorptive epithelial cells are damaged if directly exposed to SCFAs. The concept of trophic feeds is also widely accepted in clinical medicine, in particular in neonatology, where intestinal atrophy during the administration of parenteral nutrition can be devastating.

With the cloning and de-orphanization of multiple G protein-coupled receptors (GPCRs) activated by organic molecules that are either components of a meal or are generated or secreted in response to meal ingestion, much new interest has been generated in the concept of luminal chemosensing, due to molecular characterization of the luminal sensors involved. Although there have been five different tastes classically associated with the oral cavity, the gastrointestinal tract mostly expresses sweet, bitter, and *umami* (proteinaceous) taste receptors (TAS1R and TAS2R families), which are composed of GPCR heterodimers. The unique combinations of these receptor subtypes within each family confer different functionalities and thus perceptions of taste. Sweet taste receptors use a combination of TAS1R2 and TAS1R3, whereas *umami* receptors are composed of TAS1R1 and TAS1R3[7]. Bitter taste receptors utilize this second family of taste receptors, TAS2R, which have over 25 known subtypes[7].

Due to the influx of a multitude of intact and partially digested organic compounds accompanying meal ingestion, it is of keen interest to study foregut chemosensors for these compounds present in the upper intestine. Thus far GPCRs activated by long-chain FAs (FFA1 and 4, also known as GPR40 and 120), SCFAs (FFA3 and 2, also known as GPR41

and 43), and bile acids (GPBAR, also known as GPR131 or TGR5) have been identified in the intestinal luminal membrane [8].

Activation of TASRs, FFARs, and GPBAR release several bioactive peptides, including the family of GLPs, which are generated through the activity of prohormone convertase 1/3, which proteolytically cleaves proglucagon to produce GLP-1 and GLP-2 in enteroendocrine L cells[9*]. GLP-1 is an important incretin released by L cells distributed throughout the gastrointestinal tract, conventionally thought to help mediate glycemic control. GLP-2 has important trophic effects on the intestinal epithelium, including modulating crypt-villus depth, crypt cell proliferation rate, and intestinal length and weight[10*]. Furthermore, GLP-2 is expressed in other cell types within the gastrointestinal tract and central nervous system[11], supporting its function as an important intermediate in many cell-signaling pathways. GLPs are metabolized mostly by dipeptidyl peptidase IV (DPP-IV), the inhibition of which has been used clinically to enhance the effects of endogenous hormones, mostly in the treatment of diabetes[12*].

Thus, these GPCRs, particularly expressed on L cells, have been implicated in transducing the effects of meal ingestion into many postprandial metabolic effects. A schematic diagram depicting the activation of luminal-facing GPCRs expressed on enteroendocrine cells and their physiological functions is depicted as Figure 1.

Taste Receptor-Related Release of GLPs

The three taste receptors are GPCRs that are coupled with the taste signal-specific G-protein α–subunits α-gustducin and/or α-transducin, to regulate the intestinal response to the luminal content through the mechanism of nutrient chemosensing (Fig 1).

The sweet taste receptor (TAS1R2/TAS1R3) is a major glucose sensor, important to regulating glucose tolerance and the effects of insulin. Gustducin, TAS1R2 and TAS1R3, all coexpressed on GLP-2-producing L cells, are involved in the functional physiological hormonal response to sweet taste receptor ligands[13*]. In TAS1R3 knockout mice, Murovets *et al*. [14*] reported that glucose tolerance was reduced, accompanied by increased insulin resistance, indicating that this component of the sweet receptor is involved in gut sugar-sensing pathways, probably involving impaired release of GLP-1. The broad distribution of TAS1R3, with high abundance particularly in the central nervous system and pancreas, however supports extraintestinal pathways as well. New data by Shirazi-Beechey *et al*. suggests that in addition to being expressed in K cells, TAS1R2 and TAS1R3 are co-localized with GLP-2 in L cells, supported by a reported increase of GLP-1 and GLP-2 release due to TAS1R2 and TAS1R3 activation[15**].

The *umami* receptor (TAS1R1/TAS1R3), associated with the α-gustducin and α-transducin, is activated by the representative *umami* ligand monosodium glutamate and allosterically enhanced by inositol monophosphate, which activates local intestinal functions. Findings by Kendig *et al*. suggest that *umami* receptors, which are highly expressed in colonic enteroendocrine cells, specifically L cells, accelerate colonic pellet movement and the peristaltic reflex[16*]. In the foregut, luminal perfusion of *umami* receptor ligands increases the release of GLP-2, which increases the rate of bicarbonate secretion, an established

foregut mucosal protective mechanism, implicating nutrient chemosensing in the enhancement of mucosal defense mechanisms[17]. Moreover, bicarbonate secretion via *umami* receptor activation of a GLP-2-mediated pathway, which attenuates NSAID-induced intestinal damage, as reported by Inoue *et al.*, is enhanced by DPP-IV inhibition that increases circulating GLP-2 concentrations by decreasing its metabolism [18].

Finally, bitter taste receptors (TAS2Rs) exist in over 25 different subtypes, which are present either in monomer or homo-multimeric forms. The widespread variety of bitter taste receptors is likely related to the importance for organisms to avoid toxins, which are usually bitter tasting. The strength of the bitter taste correlates directly with how large a homomultimer of TAS2Rs is present[19*]. Bitter taste receptors are expressed in numerous enteroendocrine cells types – no study has been able to localize them to a specific cell type *in situ* – with extremely high expression in cultured STC-1 and NCI-H716 enteroendocrine-based cell lines, both of which also co-express α-gustducin and GLP-1 [20*,21*]. The α-subunit of G-protein coupled to bitter taste receptors, like the sweet and *umami* receptors, is also α-gustducin, which Kim *et al*. have reported increases phospholipase C activity and reduces intracellular cAMP levels, with a resultant downstream increase in intracellular calcium levels and GLP-1 release[21*]. This mode of release of the incretin GLP-1 provides the basis for novel diabetes therapies in which the bitter taste receptor serves as a molecular target.

Fatty Acid Receptor (FFAR) – Mediated GLP Release

In addition to taste receptors, FFAs have recently been implicated as important mediators of GLP release (Fig 1). FFAs are highly expressed on L cells, implying their involvement in the release of proglucagon-derived peptides. FFA1 ligands such as oleic acid activate the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway to preserve the viability of tight junctions in the intestinal epithelium[22*]. Miyamoto *et al*. reported that GLP-2 affects the function of the junctional structural proteins zonula occludens (ZO) 1–3, occludin, and the claudins, through the MAPK/ERK pathway to increase paracellular resistance to permeation of ions and small molecules, increasing epithelial integrity [22*].

The ileal-expressed FFA1 and FFA4 have been implicated in mediating GLP-2 release in Crohn's disease patients [23*], which is of importance since GLP-2 has associated anti-inflammatory effects. Although FFAR1 activation increased GLP-2 release, the pro-inflammatory mediator tumor necrosis factor (TNF)-α activated FFA4 that attenuated the beneficial anti-inflammatory effects of FFA1 dependent GLP-2 release, indicating a feedback mechanism to inhibit excess GLP-2 production[23*].

In the duodenum, the long-chain FFAR FFA1 and the short-chain FFAR FFA3 increase the rate of epithelial bicarbonate secretion through a GLP-2-dependent mechanism[24**], further implicating GLP-2 in cytoprotective mechanisms. Tanaka *et al*. have reported that DPP-IV inhibition combined with FFA1 activation synergistically increases the glucose-dependent insulin release and plasma concentration of GLP-1 [25*], and Akiba *et al*. have reported similar results using a duodenal perfusion system[24*]. These results indicate that

FFA1 mediates the release of both GLPs that maintain gut integrity. Moreover, Kawaguchi *et al*. reported that exendin-4, a DPPIV-resistant GLP-1 analogue, was an extremely effective treatment for steatohepatitis in murine models[26*], which further parallels GLP-1 and GLP-2 as important molecules in regulating inflammation, especially in the digestive organs. Whether it is through a taste or fatty acid receptor-mediated nutrient chemosensing mechanism, GLP-1 and GLP-2 release are important factors involved in mucosal defense and glycemic control.

Bile acid receptor (GPBAR)

Bile acids are endogenous cholesterol metabolites secreted into the duodenal lumen at mM concentrations in response to meal ingestion. The bile acid selective membrane-bound GPCR termed GPBAR is expressed in L cells. Oral supplementation of a synthetic GPBAR agonist prevented inflammation in a mouse colitis model via a GLP-2-mediated pathway[27*]. Unlike TASRs and FFAs, GPBAR is coupled with $G\alpha_s$, activating an intracellular cAMP- exchange protein directly activated by cAMP (Epac) signaling pathway preceding GLP release [28,29*], which can enhance glucose- or L-glutamate-evoked GLP release [28,30], implicating GPBAR in the modulation of nutrient chemosensing in L cells (Fig 1). Since GPBAR is widely expressed in many other organs such as in the gallbladder, targeting a GPBAR agonist to the intestinal receptors would likely be necessary for therapeutic applications of novel agonists [31*].

GLPs in Common Gastrointestinal Disorders

During digestion, GLP-1 release is associated with satiation [32*], essentially acting as a feedback mechanism to inhibit excess food intake, through activation of central satiety receptors present in but not limited to the hypothalamic paraventricular and arcuate nuclei. Nguyen *et al.* reported that in morbid obesity, GLP-1 release in response to intraduodenal glucose perfusion was diminished even though insulin and the release of another incretin, glucose-dependent insulinotropic polypeptide (GIP), increased, with resultant hyperinsulinemia and hyperglycemia[33*]. These results suggest that a primary defect underlying morbid obesity could be lack of post-prandial satiety due to impaired GLP-1 release.

Expression of the GLP-2 receptor (GLP-2R) in the colon and ileum are diminished in subjects with inflammatory bowel disease (IBD) [34*]. Since GLP-2 exerts anti-inflammatory effects and also increases mucosal barrier integrity, as reported by Walker *et al*. [35*], diminished GLP-2R expression could in part explain the observed diminished barrier function and inflammation in Crohn’s disease and ulcerative colitis[36]. Furthermore, Pedersen *et al.* have recently reported that GLP-2R is not expressed on the intestinal epithelium but, rather, on enteric neurons in addition to subepithelial myofibroblasts [37*], which have been implicated in the regulation of inflammation in IBD [38*].

The United States Food & Drug Administration (FDA) has recently approved the DPP-IV resistant GLP-2 analog teduglutide for the treatment of intestinal failure. In clinical trials, teduglutide has convincingly improved intestinal fluid and electrolyte absorption [39,40**].

In piglets with experimental intestinal failure, teduglutide treatment increased the overall intestinal weight per length and intestinal protein synthesis rates consistent with the trophic functions of GLP-2[41*], due to its release of growth factors such as keratinocyte growth factor (KGF) and insulin-like growth factor (IGF) from intestinal subepithelial myofibroblasts expressing GLP-2 receptors [42]. Although most of the benefit for teduglutide has been attributed to its intestinotrophic effects, its anti-inflammatory and barrier strengthening effects may be of additional benefit in the therapy of chronic inflammatory conditions, noting that teduglutide is not FDA approved for the treatment of inflammatory conditions.

Artificial Sweeteners

Exogenous GLP-2 analog administration, of proven benefit in intestinal failure, may, as discussed above, have additional benefits in IBD, functional bowel disease (FBD), and other diseases. Exogenous GLP-2 analog therapy is usually required over a prolonged period and can be quite costly. While exogenous GLP-2 analog administration has been studied thoroughly, increasing endogenous GLP-2 release has received much less clinical attention. One practical method to physiologically release endogenous GLP-2 is through the ingestion of ligands for receptors expressed on the L cell apical membrane that release GLP-2 when activated. In this regard, artificial sweeteners, which are simply high-affinity ligands for the sweet taste receptor (TASR1R2/3), release GLP-1 and GLP-2 [8,14**], with beneficial effects on glycemic control and on the intestinal mucosa. Since artificial sweeteners are in common clinical use and are recognized as food additives by the FDA, their non-FDA approved use in diabetes, FBD, and IBD deserves further study although some epidemiologic studies suggest that these substances may be ineffective or even detrimental [43].

Summary and future directions

The mechanistic basis for the observation that SCFAs and other nutrients and non-nutrients in the intestinal lumen following a meal are intestinotrophic has been unraveled by recent experimental studies in which luminal compounds activate nutrient chemosensors expressed on L cells. This specific cell type releases trophic hormones into the portal circulation and the lymphatics to activate receptors expressed on epithelial myofibroblasts that release growth factors and thus activate enterocyte-expressed receptors, increasing the proliferation rate of intestinal stem cells. The discovery of the many luminal nutrient sensors has provided numerous molecular targets on which novel therapies with low risk of side effects for intestinal failure, diabetes, obesity, FBD, and IBD can be based.

Acknowledgments

Financial support and sponsorship

This work was supported by research grants form the Department of Veterans Affairsand the National Institutes of Health.

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Key Points

- Taste Receptors (TASRs) are expressed throughout the gastrointestinal tract and mediate GLP release
- Free fatty acids (FFAs) expressed on L cells modulate GLP release and act as important regulators of nutrient chemosensing
- The membrane bile acid receptor (GPBAR) expressed on L cells alters GLP release activated by TASRs and FFAs.
- Glucagon-like peptides (GLPs) are responsible for maintaining intestinal integrity and growth as well as sugar uptake

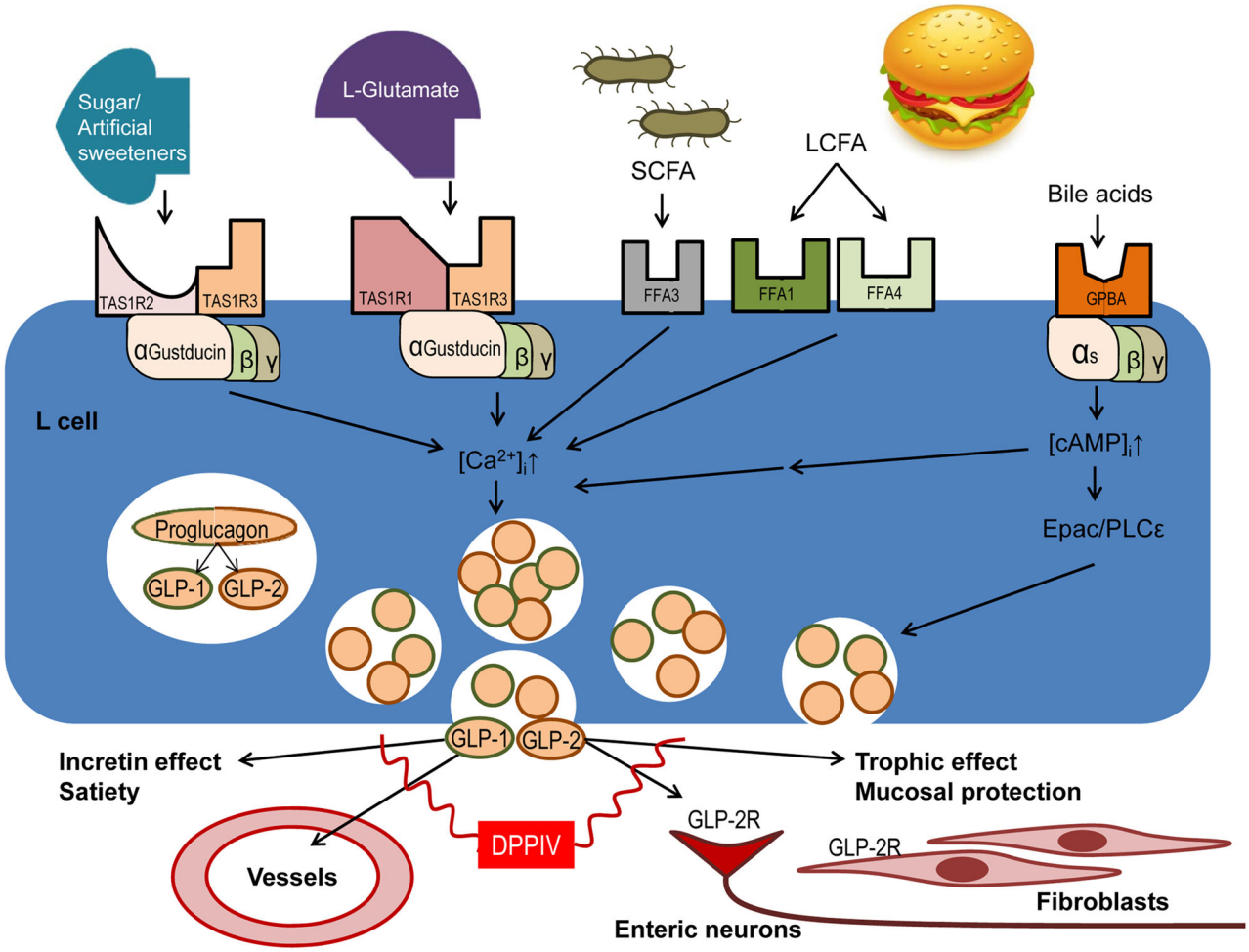

Figure 1.

Several nutrient-sensing GPCRs are expressed on the apical membrane of L cells. Receptor activation releases GLP mediated by an increase in intracellular calcium concentration ([Ca^{2+}]i). Taste receptors (TAS1R heterodimers) are coupled with α-gustducin, whereas the bile acid receptor (GPBAR) is coupled with $G_{\alpha i}$, enhancing the TAS1R-mediated signal. Released GLP-1 and GLP-2 have many functions mediated via distinct receptors expressed on target organs such as enteric neurons and subepithelial myofibroblasts.