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Gastrointestinal defense mechanisms

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Journal

ISSN

Authors

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Publication Date

DOI

Peer reviewed

CURRENT OPINION   Gastrointestinal defense mechanisms

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Purpose of review
To summarize and illuminate the recent findings regarding gastroduodenal mucosal defense mechanisms and the specific biomolecules involved in regulating this process, such as glucagon-like peptides (GLPs).

Recent findings
There has been a growing interest in luminal nutrient chemosensing and its physiological effects throughout the digestive system. From the ingestion of food in the oral cavity to the processing and absorption of nutrients in the intestines, nutrient chemosensing receptors signal the production and release of numerous bioactive peptides from enteroendocrine cells, such as the proglucagon-derived peptides. There has been a major emphasis on two proglucagon-derived peptides, namely GLP-1 and GLP-2, due to their apparent beneficial effect on gut structure, function, and on metabolic processes. As an incretin, GLP-1 not only enhances the effect and release of insulin on pancreatic βcells but also has been implicated in having trophic effects on the intestinal epithelium. In addition, GLP-2, the other major proglucagon-derived peptide, has potent intestinotrophic effects, such as increasing the rate of mucosal stem cell proliferation, mucosal blood flow, and fluid absorption, as well as augmenting the rate of duodenal bicarbonate secretion to improve gastric mucosal health and longevity.

Summary
Understanding the mechanisms underlying nutrient chemosensing and how it relates to GLP release can further elucidate how the gut functions in response to cellular changes and disturbances. Furthermore, a more in-depth comprehension of GLP release and its tissue-specific effects will help improve the utility of GLP-1 and GLP-2 receptor agonists in clinical settings. This, in turn, should help patients suffering from intestinal failure, malabsorption, and mucosal injury.

Keywords
free fatty acid receptors, gastric mucosal defense, glucagon-like peptides, gut taste receptors, nutrient chemosensing, trophic feeds

INTRODUCTION

Over the past decade, many findings and phenomena have been discovered regarding luminal nutrient absorption and the clinical intervention known as 'trophic feeding', used to perfuse nutrients, often at low rates, into the gut lumen and thus promote gut health. More recent studies have suggested that the luminal nutrients contained in these feeds trigger a signaling cascade that releases gut hormones, which subsequently lead to the mucosal protective effects observed in the gastrointestinal tract [1]. In this review, we aim to support this hypothesis through a thorough summary of recent findings regarding gut hormones and their release following mucosal exposure to luminal nutrients. These findings are important not only for establishing the mechanism behind the success of trophic feeds but also for identifying which nutrients may optimally regenerate enterocytes and reestablish overall gut health.

To address this point, it is important to understand the interplay between trophic feeding and nutrient chemosensing, the cellular process of recognizing luminal nutrients present in the gut lumen that involves specific taste receptors. Unlike the oral cavity, which contains five distinct classes of taste receptors, the intestines only express three: *umami* (proteinaceous), sweet, and bitter, the latter containing a multitude of subclasses. Each of these

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KEY POINTS

- Glucagon-like peptides (GLPs) play an important role in intestinal regeneration and growth as well as glucose metabolism.

- Taste receptors (TASRs) are expressed not only in the oral microflora but throughout the gastrointestinal tract and have been implicated in incretin release and promoting gut health.

- Free fatty acid receptors (FFARs) have been co-localized to enteroendocrine cells with GLPs and help mediate their release as a part of a wider nutrient chemosensing process.

- Bile acid receptors expressed on L cells modulate TASR and FFAR-dependent GLP release.

receptors is a G-protein coupled receptor (GPCR) heterodimer, comprising combinations of members of taste receptor families (TAS1R and TAS2R), which result in distinct and discrete perceptions of taste [2▪]. *Umami* receptors comprise TAS1R1 and TAS1R3, whereas sweet taste receptors combine TAS1R2 and TAS1R3 [3]. In addition to this first family (TAS1R) of taste receptors, there is a second type (TAS2R) that is utilized exclusively by bitter taste receptors. There are over 25 known human subtypes of TAS2Rs, conferring over 300 possible GPCR heterodimers [4]. Similar to the oral taste receptors, taste receptors in the gut are responsible for maintaining energy balance and glycemic control during digestive processes. To accomplish this goal, taste receptors signal the release of a large variety of paracrine and endocrine gut hormones that elicit functional physiological responses throughout the gastrointestinal tract [5]. Together, taste receptors coupled to hormone release help maintain metabolic processes, release gut hormones, and ultimately promote intestinal health.

In addition to taste receptors, there are a wide variety of biomolecules that elicit a physiological response through activation of nutrient chemosensors. One such group of molecules is fatty acids (FAs), which are sensed by specific and distinct GPCRs based on the length of the respective carbon tail. Two such classes are short-chain FAs (SCFAs) and long-chain FAs (LCFAs), which are shorter than eight and longer than 16 carbons, respectively. An important early study conducted by Kripke's group in 1989 [6] suggested that exogenous SCFA infusion was trophic for the intestine, in particular by increasing the rate of mucosal cell growth and accelerating maturation of the villous cells. Because SCFAs are generated by the oral microflora in addition to the gut flora, an acute load of these

endogenously-produced FAs may be sufficient to release gut hormones, further implicating exogenous SCFAs as possible therapeutic mucosal agents with the ultimate aim of repairing intestinal damage. Additional studies that parallel Kripke's findings also support the concept of SCFA-induced intestinal mucosal growth. In a piglet model, SCFA-induced trophic effects occurred in portions of the intestine not originally exposed to the SCFA infusions, suggesting that these trophic effects did not require direct mucosal exposure [7]. Although there is ample evidence to support the notion that SCFAs signal mucosal protective effects, it has been previously widely accepted that the trophic effects of SCFAs, specifically butyrate, are mainly derived from fueling enterocyte growth [8]. This school of thought was based on prior observations that epithelial cells absorb SCFAs and are damaged when directly exposed to high concentrations SCFAs *in vitro*, before the discovery of SCFA-specific GPCRs. The concept of trophic feeds has subsequently been widely established and implemented clinically; luminal exposure to small amounts of SCFAs may thus be useful in patients receiving parenteral nutrition due to their prevention of the mucosal atrophy that occurs in the absence of luminal nutrients.

Two major similarities between TASRs and free FA receptors (FFARs) are the observation that their activation reverses mucosal atrophy and maintains appropriate glucose metabolism when activated, effects that are at least partially mediated by glucagon-like peptides (GLPs). These biomolecules are proteolytically cleaved from proglucagon via prohormone convertase 1/3, a process responsible for the production of the two peptides expressed in enteroendocrine L-cells: GLP-1 and GLP-2 [8]. GLP-1 is highly expressed in enteroendocrine L-cells throughout the gastrointestinal tract, where it serves as an incretin that helps maintain glycemic control. Like GLP-1, GLP-2, also expressed in L-cells, has many intestinotrophic properties, such as increasing the rate of crypt enterocyte proliferation, increasing the rate of mesenteric artery blood flow, and increasing crypt-villus depth [9▪]. The GLP-2 receptor (GLP-2R) is expressed in subepithelial pericryptal myofibroblasts and enteric neurons, which further support its proposed function as major intermediate in many cell-signaling pathways [10,11]. Amongst other functions, many of these pathways are believed to decrease inflammation in gastrointestinal, hepatic, pulmonary, and muscular tissues [12▪]. The proteolytic enzyme dipeptidyl peptidase IV (DPPIV) has major specificity for GLP hormones, governing their plasma $t_{1/2}$. DPPIV inhibition, by increasing the plasma $t_{1/2}$ of GLP-1, is used clinically in the treatment of type 2 diabetes [13,14▪,15▪] and

may be potentially considered as a treatment for short-bowel syndrome due to its prolongation of the plasma $t_{1/2}$ of GLP-2 [16].

In short, exploration of nutrient chemosensing and responses is integral for understanding gut metabolic processes and control of growth. The effects of activation of these L-cell expressed GPCRs on intestinal mucosal growth, specifically through a GLP-dependent mechanism, may eventually lead to the development of novel nutrient receptor ligands used in the therapy of important gastrointestinal diseases such as short-gut syndrome and diseases associated with a 'leaky gut' [17].

TASTE RECEPTOR-RELATED RELEASE OF GLUCAGON-LIKE PEPTIDES

Each intestinal taste receptor is a GPCR heterodimer that includes an important G-protein subunit, α-gustducin, which is responsible for nutrient chemosensing and subsequent intestinal response.

The sweet taste receptor, a TAS1R2/TAS1R3 heterodimer, serves as a blood glucose sensor important for facilitating glycemic control. Expressed on brush and enteroendocrine cells, sweet taste receptors are present throughout the gastrointestinal tract, linked to ghrelin and GLP-1 production [18]. In a clinical study, Maruoka *et al.* [19■] demonstrated that treatment with mosapride citrate, a prokinetic compound, and a 5-HT$_4$ receptor agonist increased GLP-1 and serum insulin concentrations. This incretin increase was also accompanied by increased TAS1R2/TAS1R3 expression, which further implicates sweet taste receptors in GLP-1 and subsequent insulin release [19■]. In addition to GLP-1, a previous study by Moran *et al.* [20] implicated GLP-2 as a major product of sweet taste receptor activation; treatment artificial sweeteners, which are high-affinity TAS1R2/TAS1R3 receptor agonists, increased GLP-2 concentrations and sodium–glucose co-transporter 1 (SGLT1) expression in a model system. SGLT1 expression is of major interest, because it is believed to drive glucose-dependent GLP-1 release [21]. Therefore, it appears that both GLP-1 and GLP-2 are released in response to sweet-taste receptor activation, further supported by the observation that GLP-1, GLP-2, TAS1R2/TAS1R3, and α-gustducin are all expressed in or on L-cells [22■]. These specific enteroendocrine cells may thus transduce the numerous physiological responses that occur in response to sweet taste receptor activation. Finally, although TAS1R2/TAS1R3 activation may delay the progression of several gastrointestinal diseases, a new study by Ohtsu *et al.* [23] demonstrated that artificial sweeteners and other sweet taste receptor agonists might activate substantially different intracellular signaling pathways. Hutu-80 cells responded differently to the four sweeteners sucralose, saccharin, acesulfame K, and glycyrrhizin, manifest as highly variable Ca^{2+} and cyclic adenosine monophosphate concentrations observed posttreatment, perhaps due to binding to different regions of the *umami* receptor [24]. As this variability may have marked clinical effects, further studies of the binding kinetics and functional physiological response of sweet taste receptor activation due to synthetic agonists is of likely value.

The *umami* taste receptor that senses protein-derived substances is composed of a TAS1R1/TAS1R3 heterodimer associated with α-gustducin and α-transducin subunits. Although this amino acid receptor is believed to affect insulin production and glycemic control, it has classically been thought to have a more potent intestinotrophic and mucosal protective effects through release of intestinal hormones and by increasing the rate of duodenal bicarbonate secretion, at least partially mediated by GLP-2, which is released from *umami* receptor expressing L-cells [25]. These findings implicate nutrient chemosensing as a means to enhance mucosal defenses. Although *umami* receptor components have evolutionarily conserved sequences, their expression varies widely dependent on the presence of distinct metabolic processes. For example, skeletal muscle components MyoD and myogenin modulate TAS1R3 promoter activity with consequent muscle growth and metabolism, which in turn affects intestinal *umami* receptor expression and nutrient chemosensing in the intestines [25]. This variation in receptor expression may affect intestinal physiology, such as the peristaltic movement of the colonic content and the peristaltic reflex – both of which are accelerated via *umami* receptor activation [26■]. Finally, *umami* receptor agonists may be important to include in trophic feeds according to the findings of Yoshida *et al.* [27], who *suggest* that the synergism that occurs between the *umami* ligands glutamate and 5' ribonucleotides may increase the palatability of multiple food sources and not only increase the volume of feeds, but, by strongly activating mucosal *umami* receptors expressed on L cells, enhances mucosal defense mechanisms.

FREE FATTY ACID RECEPTOR–MEDIATED GLUCAGON-LIKE PEPTIDE RELEASE

Although there appear to be many biomolecular pathways that release GLP, FFARs are a specific family of receptors that have also been implicated as important molecules for maintaining gut health and growth. Throughout the gastrointestinal tract,

FFARs are expressed in enteroendocrine cells, especially L-cells, which are also involved in releasing proglucagon-derived peptides [28,29].

Although the SCFA receptors G-protein receptor (GPR)41 and 43 promote intestinal growth, each utilizes different downstream mechanisms for achieving the same end effects: promoting intestinal regeneration and growth. This process includes upregulating duodenal bicarbonate secretion via a calcium-sensing receptor dependent mechanism, as well as increasing the rates of intestinal electrolyte uptake and mucosal blood flow [30,31]. GPR41 (FFAR3) was recently identified as an important nutrient chemosensor transducing GLP-2 release from duodenal L-cells [32], associated with an increase in the rate of duodenal mucosal bicarbonate secretion (DBS). GPR43 (FFAR2) activation also increased the rate of DBS, believed to be independent of GLP-2 release and occurring through serotonin-dependent pathways [33■]. Although GPR43 activation increases DBS independently of GLP-2 pathways, Psichas et al. [34■] co-localized GPR43 with GLP-1 and PYY on L-cells, reporting that activation of GPR43 substantially increases the release of these satiety-inducing products. This GPR41-dependent increase in GLP-1 may be mediated by a mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway [35]. Together, these findings highlight the mechanistic differences between GPR41 and 43 activation, emphasizing the importance of using specific SCFA receptor agonists for clinical studies.

In addition to SCFAs, the LCFA receptors GPR40 and 120 (FFAR1 and 4) may also be important components of hypothetical therapeutic tools intended for the healing of intestinal damage. Like GPR41 and 43, these two LCFA receptors are expressed throughout the gastrointestinal tract, as well as on enteric neurons, with a very high level of expression on enteroendocrine L-cells [36,37]. Interestingly, a study conducted by Miyamoto et al. [38■] reported that like GPR41, GPR40 (FFAR1) releases GLP-1 and insulin through activation of MAPK, also termed ERK pathway. Although this finding highlights one of the multiple overlaps between SCFAs and LCFAs with regard to nutrient chemosensing pathways, it is still widely accepted that the LCFA receptors GPR40 and 120 are involved in the regulation of insulin production and glucose metabolism to a greater extent than their SCFA receptor counterparts. Inactivation of GPR40 and 120 signaling by mercaptoacetate decreased GLP-1 release and serum insulin concentrations, with consequent hyperglycemia, further strengthening the notion that LCFA receptor activation is linked to GLP-1 release. Inactivation of GPR40 and possibly 120 signaling by mercaptoacetate was also proposed as an explanation for the increased feeding behavior associated with inhibition of FA oxidation [39]. There may be a dependency or synergism between GPR40 and 120 with regard to controlling satiety. Sclafani et al. [40] reported that knocking out both LCFA receptors significantly increased fat-induced appetite, attenuated by knocking out the receptors singly. This newly discovered putative interaction between GPR40 and 120 should encourage the conduct of more studies regarding their individual and combined effects on satiety, blood glucose levels, and GLP release.

CLINICAL TRIALS WITH GLUCAGON-LIKE PEPTIDES

Due to their effects regarding mucosal protection and glycemic control, GLPs are beginning to be used widely in clinical trials aimed at reducing the ill effects of many gastrointestinal diseases. Teduglutide, a synthetic DPPIV-resistant GLP-2 receptor (GLP2R) agonist, has become increasingly popular in treating the short bowel syndrome. In a clinical trial, Iturrino et al. [41■] reported that a 7-day treatment with teduglutide in parenteral nutrition-dependent adults with short bowel syndrome significantly improved monosaccharide absorption and intestinal fluid balance, as well as increased bowel transit time. These findings are further supported by a rodent study that examined the effects of GLP-2, growth hormone, and keratinocyte growth factor on intestinal growth after small bowel resection. Here, Gu et al. reported that GLP-2 had potent trophic effects on the intestinal mucosa, supporting it as a major component in reestablishing gut health. These promising studies are just a few of many examples in which GLP-2 analogs have had profound beneficial effects on the gut mucosa, underlying the recent FDA approval of the DPPIV-resistant analog teduglutide for the therapy of short-gut syndrome [42]. Like GLP-2 analogs, GLP-1 receptor (GLP1R) agonists are also being tested in their capacity to reconstitute gut health. Although further studies are necessary to delineate the effects of GLP1R and GLP2R agonists in specific gastrointestinal diseases, the current initial findings are promising.

Even though most patients who are diagnosed with nonsteroidal anti-inflammatory drug (NSAID)-induced enteropathy are usually asymptomatic, intestinal damage due to the overuse of NSAIDs is a major problem and can be the gateway to other, more serious intestinal injuries. Fujiwara's group reported that DPPIV inhibition, when combined with an elemental diet, significantly reduced

indomethacin-induced intestinal injury. These findings, as well as many others, suggest that the increased $t_{1/2}$ of endogenous GLP-2 that occurs with DPPIV inhibition decreases the intestinal injury associated with prolonged NSAID use [43▪], a difficult-to-treat condition. Many investigators are now considering using DPPIV inhibitors to maximize the effects of endogenous and exogenous GLPs in nondiabetic individuals, as DPPIV inhibition in and of itself does not cause hypoglycemia in normoglycemic, nondiabetic individuals [44,45].

CONCLUSION

Recent investigations suggest that activation of nutrient chemosensors expressed on enteroendocrine cells, such as taste and SCFA receptors, promote mucosal protection via the release of trophic gut hormones, like GLPs, that are released into the portal circulation, activating receptors expressed on enteric neurons and myofibroblasts. These receptors then release growth factors that significantly increase intestinal stem-cell proliferation and promote overall intestinal growth and health. The recent discoveries involving this wide variety of luminal nutrient chemosensors has provided a number of new possibilities for creating novel therapies to treat mucosal damage and short bowel syndrome.

Conflicts of interest

There are no conflicts of interest.

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