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Review

GLP-2: What do we know? What are we going to discover?

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ABSTRACT

Glucagon-like peptide 2 [GLP-2] is a 33-amino acid peptide released from the mucosal enteroendocrine L-cells of the intestine. The actions of GLP-2 are transduced by the GLP-2 receptor [GLP-2R], which is localized in the neurons of the enteric nervous system but not in the intestinal epithelium, indicating an indirect mechanism of action. GLP-2 is well known for its trophic role within the intestine and interest in GLP-2 is now reviving based on the approval of the GLP-2R agonist for treatment of short bowel syndrome [SBS]. Recently it also seems to be involved in glucose homeostasis.

The aim of this review is to outline the importance of neuroendocrine peptides, specifically of GLP-2 in the enteric modulation of the gastrointestinal function and to focus on new works in order to present an innovative picture of GLP-2.

Contents

1. Introduction

Most of the currently known gut hormones were discovered in the 1980s [1]. However, glucagon-like substances in extracts of intestinal mucosa had already been described in 1948 [2]. Up to now hormones continue to be intensely studied such as the products of proglucagnon including glucagon, oxyntomodulin [OXM] and proglucagon derived peptides 1 [GLP-1], and 2 [GLP-2]. [3]. Glucagon is a counter-regulatory hormone to insulin and acts in response to hypoglycemia while GLP-1 is a potent incretin hormone which also inhibits glucagon secretion [3,4]. GLP-1, in addition to inducing the secretion of insulin, has been shown to have biological effects on the gastrointestinal functions in both animals [5–7] and humans [8–10]. Glucagon and GLP-1 have been studied more than OXM and GLP-2, probably because of their role in the regulation of glucose homeostasis. Anyway, both OXM and GLP-2 have interesting biology. OXM seems to be a dual agonist of both the glucagon-like peptide-1 receptor (GLP1R) and the glucagon receptor (GCGR) and is involved in energetic and glucose metabolism. It lowers food intake, increases energy expenditure and improves glucose metabolism [11]. However, the mechanisms of actions are not fully understood and it is still unclear if additional G- protein-coupled receptors are engaged in the lowering of body weight and glucose as well as GCGR and GLP-1R. Thus, further studies are required to completely understand the mechanism of action.

GLP-2 is well known for its trophic role within the intestine [12] and interest in GLP-2 is now reviving, based on the approval of the GLP-2R agonist for treatment of short bowel syndrome [SBS] [13]. Recently it also seems to be involved in the maintaining of glucose homeostasis [14,15]. However, GLP-2 plays a multifaceted role within the intestine [16] and the overwhelming interest attracted by GLP-2 as a trophic

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factor has somewhat clouded the importance of the peptide in other gastrointestinal processes.

This review focuses on the recent insights into the action of GLP-2 involving the enteric nervous system [ENS] in order to outline its importance in the neural modulation of the gastrointestinal function and to present an innovative picture of GLP-2 after the approval, by the European Medicines Agency and the US Food and Drug Administration, of the GLP-2R agonist, teduglutide.

2. GLP-2 as a neuroendocrine signal from the gastrointestinal tract

GLP-2 belongs to the GI hormone class and more specifically it is a 33-amino acid peptide that is secreted following nutrient ingestion by the intestinal endocrine L cell through the cleavage of proglucagon prohormone convertase 1/3. The GLP-2 action is initiated by binding to its specific receptor, the GLP-2R that belongs to the class of seven transmembrane- G protein-coupled receptors [16] and determines the activation of cAMP protein Kinase -dependent pathway [17]. However, GLP-2R has the ability to couple to different G protein subunits and to activate multiple signalling pathways [18]. Studies using cells that naturally express the receptor suggest that phosphatidylinositol 3-kinase-γ[PI3Kγ] and subsequent Akt phosphorylation are the intracellular pathways activated by GLP-2 [19,20]. The enteric nervous system seems to be a key component in the GLP-2 action, and this was initially evident for one of the GLP-2's main activities, namely its ability to enhance intestinal epithelial growth. The enteric neurons express the receptor [21–24] and the GLP-2R activation is able to stimulate gut epithelial growth and repair. In fact, the signal is transduced by the GLP-2R on enteric neurons and is then transmitted back to the epithelium [23]. On the contrary, in a model of partial enteric nervous deficit, the glial cell line-derived neurotropic factor family receptor alpha [2] [GFRα2] knockout mouse, the loss of GFRα2 did not affect its trophic action [25], suggesting that a functional ENS is not essential to preserve this activity. However, compensation in a transgenic model is common. Thus, it may also be possible that compensatory mechanisms are triggered.

The GLP-2R is expressed by myofibroblasts [26] and it was hypothesized that GLP-2 exerts its trophic actions indirectly through myofibroblasts as well. Indeed, GLP-2 signalling induces the release of several growth factors such us insulin-like growth factor-1 and keratinocyte growth factor, that are responsible for the proliferative effects of GLP-2.

3. GLP-2 in the gastrointestinal function

The presence of GLP-2R in the ENS [21–24] has suggested that some of the GLP-2 actions within the gut may not be direct in the regulation of the gastrointestinal [GI] function.

Later studies have confirmed that GLP-2 affects gut motor activity through modulation of the ENS [27,28] with the final purpose of slowing motility in order to contribute and promote intestinal absorption. In the mouse small intestine GLP-2 reduces the spontaneous smooth muscle activity by increasing nitric oxide releases [22] while in the colon, where the GLP-2R is expressed and colocalized with acetylcholine -IR neurons of the myenteric plexus, the peptide acts by slowing the motility through inhibition of acetylcholine release from enteric neurons [28] suggesting a paracrine mechanism of action. A functional ENS seems to be essential for the GLP-2 motor action. Therefore, in the model of partial enteric nervous deficit, the [GFRα2] knockout mouse, GLP-2 was not able to inhibit GI transit [25].

In the mouse stomach, in vitro, the exogenous administration of GLP-2 induces gastric relaxation by neural prejunctional release of vasoactive intestinal polypeptide [VIP], leading to an increase in the stomach capacity. The effect is confined to the fundus [27]. The GLP-2 action on gastric fundus seems particularly interesting because it could represent a signalling of satiety which well fits in with the finding that GLP-2 is a chemical mediator inhibiting rodent feeding behaviour [29,30]. Thus, it is likely that the GLP-2 ability to decrease gastric motility, apart from delaying the flow through the pylorus and prolonging the gastric emptying time, may also be part of the premature inhibition of further ingestion as it constitutes a prandial satiety signal. Gastric distension inhibits food intake via vagal afferent neurons through mechanisms independent of nutrient status and the GLP-2R is localized in the cell bodies of vagal afferents in the nodose ganglion [31,32]. This idea is also supported by the finding that in pigs, GLP-2 is able to reduce the vagally induced antral motility [33]. However, its effect on gastric emptying in humans appears minimal [34]. Moreover, although the peripheral administration of GLP-2 reduces short term food intake in mice [29], it is still unclear if this effect can be related to its action within the GI tract. By peripheral administration, the neuropeptides label the blood–brain barrier-free area postrema and diffuse into the adjacent regions [35]. GLP-2R is expressed also in key regions of the brain including the hypothalamus and the hippocampus [30,36]. In the hypothalamus the activation of the GLP-2R reduces gastric emptying probably through the melanocortin system [37].

It is interesting to note that diet induced obese mice are less sensitive to the GLP-2 mediated short term reduction of food intake [29]. They also display increased levels of the plasma peptide [38] and of the GLP-2R expression in the stomach [39]. These results suggest that a deregulation of the GLP-2/GLP-2R system following chronic high fat diet probably occurs.

The peptide also affects the secretory function of the GI tract. In humans, GLP-2 is capable of inhibiting both pentagastrin-stimulated and sham feeding-stimulated human gastric acid secretion [40,41], likely counteracting the parasympathetic stimulation of the stomach. In the guinea pig GLP-2 modulates enteric mucosal chloride secretion. Specifically, in the small intestine GLP-2 acts on the GLP-2R, expressed in the submucosal plexus, to suppress acetylcholine release. This action of GLP-2 reduces the liquidity in the intestinal lumen by decreasing the secretion of NaCl and H_2O [21]. Thus, GLP-2 is likely to act in a paracrine mode to influence intestinal function, via ENS and in a hormonal mode to influence gastric function.

4. GLP-2 in the ENS during inflammation

GLP-2 protects the ENS during mucosal inflammation [42,43]. Usually, during intestinal inflammation there is a decrease in the numbers of submucosal and myenteric neurons and changes to enteric glial cells within the enteric ganglia. These acute changes in neuronal cell numbers are accompanied by changes in specific neuronal activity, including the integrated motor and secretory functions of the intestine [44]. GLP-2 in this state is able to enhance survival of the enteric neurons in culture and to counteract mast cell induced neuronal cell death [45]. Moreover, in a culture of submucosal plexus neurons, GLP-2 is able to influence the profile of expression of the enteric neurons [46]. This suggests that GLP-2-induced neuroprotection of enteric neurons is mediated by direct stimulation of neuronal GLP-2R. However, experimental evidence has led to the proposal that GLP-2 effects could involve different indirect mediators and diverse signalling pathways [47]. One such mediator in both physiological and inflammatory conditions is VIP [27,42,43]. GLP-2 reduces intestinal mucosal inflammation by activation of VIP neurons in the submucosal plexus independent of any proliferative effects [43]. It restores the enteric neuronal populations to normal and influences the number and proportion of VIP-expressing neurons within the colonic submucosal plexus in vivo [42]. The GLP-2 ability to stimulate a neuronal phenotype, increasing VIP expression in primary culture of cells deriving from the submucosal plexus [46] has led to the idea that GLP-2 might also be involved in regulating the development of the ENS. In fact, a high level of expression of both hormone and receptor has been shown in the immature gut of human infants and mouse models in the later phases of gestation, when intestinal development is maximal [48,49]. Thus, it is possible to speculate that a deficit in GLP-2 production could be involved