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Review

Influence of glucagon-like peptide 2 on energy homeostasis

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ABSTRACT

Glucagon like peptide-2 (GLP-2) is a gastrointestinal hormone released from enteroendocrine L-type cells together with glucagon like peptide-1 in response to dietary nutrients. GLP-2 acts through a specific receptor, the GLP-2 receptor, mainly located in the gut and in the brain. Classically, GLP-2 is considered a trophic hormone involved in the maintenance of intestinal epithelial morphology and function. This role has been targeted for therapies promoting repair and adaptive growth of the intestinal mucosa. Recently, GLP-2 has been shown to exert beneficial effects on glucose metabolism specially in conditions related to increased uptake of energy, such as obesity. Several actions of GLP-2 are related to a positive energy balance: GLP-2 increases not only the absorptive surface, but also expression and activity of epithelial brush-border nutrient transporters and digestive enzymes, intestinal blood flow, postprandial chylomicron secretion and it inhibits gastrointestinal motility, providing the opportunity to increase absorption of nutrients. Other actions, including anorexigenic effects, appear in opposition to the energy intake. In this review, we discuss the GLP-2 functions related to energy homeostasis. GLP-2 could be considered an hormone causing positive energy balance, which, however has the role to mitigate the metabolic dysfunctions associated with hyper-adiposity.

Contents

1. Introduction

Glucagon-like peptide 2 (GLP-2) is a peptide derived from the cleavage of proglucagon, which is a prohormone mainly expressed in alpha pancreatic cells, intestinal enteroendocrine L-type cells of ileal and colonic mucosa and in the brain. In pancreas, proglucagon is cleaved by the prohormone convertase (PC)-2 to generate mainly glucagon, whereas the cleavage by PC1/3 leads to the formation of glucagon-like peptide 1 (GLP-1), GLP-2, and other small peptides in the gut endocrine cells and in brain neurons [47]. Mice null for the gene of prohormone convertases that process proglucagon to GLP-1 and GLP-2 (Pcsk1) do not produce GLP-1 or GLP-2 and are smaller (reduced weight and length gain) than wild-type controls, suggesting the importance of these peptides for energy and/or control [81]. GLP-1 facilitates insulin release during hyperglycaemia acting as an incretin, it increases insulin synthesis and may reduce the glycaemia postprandial excursion through reduction of gastric emptying [8,30,63]. For these reasons various GLP-1 analogues or inhibitors of dipeptidyl-peptidase (DPP)-4, which cleaves GLP-1, have been developed for the type 2 diabetes treatment [32]. The main biological actions of GLP-2 are related to

Abbreviations: GLP-1, glucagon-like peptide 1; GLP-2, glucagon-like peptide 2; GLP-2R, GLP-2 receptor; HFD, high fat diet; PC, prohormone convertase; POMC, proopiomelanocortin.

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the regulation of energy absorption and maintenance of mucosal morphology and integrity of the intestine [33], therefore GLP-2 analogue development has been addressed for the treatment of gastrointestinal disease, such as short bowel syndrome, inflammatory bowel disease and chemotherapeutically-induced mucositis [10,50,77]. However, although GLP-2 has not been reported to modulate insulin secretion [58,67], recent data have provided evidence for beneficial effects of GLP-2 on glucose metabolism, particularly in obese mice [3,9,11,15,22,36,68]. This review provides a brief overview on physiological effects of GLP-2 and highlights biological actions related to energy homeostasis.

2. GLP-2 biology

GLP-1 and GLP-2 are colocalized in the same secretory granule of mammalian and avian intestinal L-cells [56,75]. However, in the mammalian intestine GLP-1 and GLP-2 are secreted by the same cells in an equimolar ratio [18], whereas hypothesis of separate secretion of these two hormones from the same cells has been advanced for chicken [56]. The mechanisms that govern the sorting of proglucagon into secretory granules have been studied only from a couple of years [35,39]. Differently from other prohormones in which sorting depends on specific prodomains, the proglucagon sorting is directed by domains within GLP-1 sequence [39]. In fact, biophysical experiments showed that GLP-2 is not sorted efficiently into secretory granules and it may instead be directed towards another vesicle compartments in PC12 cultured cells [39]. Anyway, intestinal L-cells release GLP-2 following a meal ingestion in response to luminal nutrient especially carbohydrates and lipids, in particular short-chain fatty acid [18].

The mechanisms by which nutrients induce the release of peptides from the enteroendocrine cells have not been fully elucidated. Because GLP-2 is released in parallel with GLP-1 in mammalian, factors that influence GLP-1 secretion are thought to be the same for GLP-2. Different nutrient-sensing receptors are present on the mucosal membrane of L-type enteroendocrine cells, including umami taste receptor (T1R1-T1R3), sweet taste receptor (TIR2-TIR3), bile acid receptor (TGR5) and free fatty acid receptors (GPR40, GPR41, GPR43 and GPR120) [2]. The location of these chemoreceptors provides a basis for explaining how specific nutrients may regulate their absorption and the hormonal release. For example, glucose or artificial sweetener sucralose has been reported to increase GLP-2 secretion in small intestine through interaction with sweet taste receptors [28]. GLP-2, in turn may lead to upregulation in the enterocyte expression of intestinal Na^+/glucose cotransporter, SGLT1, and increased intestinal glucose absorption [24,27,61,64]. Moreover the activation of the umami receptor by glutamate stimulates GLP-2 release [78] and this may explain why dietary glutamate or glutamine supplementation improves gut functions in pigs [26]. Therefore, further information on the release mechanisms would be useful to obtain treatments by which luminal nutrients stimulating the release of GLP-1and GLP-2 affect the mucosal protection, appetite, satiety, and metabolic disorders.

After its release, GLP-2 is quickly degraded through cleavage of N-terminal histidine and alanine the by dipeptidyl peptidase-IV (DPP-IV), consequently the half-life of intravenous GLP-2 is very short, about 7 min in healthy humans [40]. The substitution of alanine with glycine as in teduglutide avoids degradation and confers greater biological activity [49]. The cleavage produces the GLP-2(3-33) [19], that can work as an antagonist of the GLP-2 receptors in rodents [12,15,69]. The GLP-2 effects are mediated by the interaction with a specific GLP-2 receptor (GLP-2R), which is a G protein-coupled receptor expressed mainly in the gut and in the brain [38,53,80]. In mice, GLP-2R–mRNA has been demonstrated with high levels of expression in the bowel [80] and recently the GLP-2R protein has been demonstrated throughout the mouse gastrointestinal tract, with higher expression in the gastric fundus and colon [5]. Indeed, GLP-2R mRNA transcripts have been detected also in heart, liver and adipose tissue [6,34]. It is interesting to note that gut GLP-2R expression may be down-regulated or upregulated by fasting or by chronic high-fat feeding, respectively [12,62].

3. GLP-2 and energy homeostasis

The GLP-2 main actions related to energy homeostasis concern the gut, the food intake and the influence on glucose metabolism.

3.1. Gut

The key action of GLP-2 is represented by its ability of increasing the intestinal absorptive mucosal surface. In fact GLP-2 was discovered as an intestinotrophic factor in 1996 [31] and it is now well clear that the peptide promotes energy absorption within gastrointestinal tract through nonspecific and specific adaptation. GLP-2 has been shown to induce crypt cell proliferation and inhibition of apoptosis and to promote the growth and regenerative repair after injury of intestinal mucosa [20,31,73,74]. The association between GLP-2 and trophic action has been found also in pathological conditions, such as post-resection intestinal adaptation, celiac disease, intestinal atrophy induced by parenteral nutrition, inflammatory bowel disease and diet-induced obesity [12,21,23,48,65]. More specifically, in murine small intestine a chronic exposition to high fat diet (HFD) induces mucosal changes consisting in increase in the crypth-villus height, which are significantly reduced after chronic administration of GLP-2 (3-33), suggesting that endogenous GLP-2 is involved in the trophic response of murine gut to HFD [12].

Besides the intestinotrophic action, several actions of GLP-2 in the gastrointestinal tract are related to promotion of energy absorption. GLP-2 increases the mesenteric blood flow [17,37] and the uptake of nutrients, by augmenting the activity and/or the expression of hexose and peptide transporters [7,24,46] and the expression of different enzymes involved in digestion [59,60]. GLP-2 has been reported also to be involved in the regulation of postprandial lipid serum concentration: it facilitates lipid intestinal absorption through an action on fatty acid translocase [45,54] and it enhances chylomicron secretion [29,41,45,54]. However, a recent study suggested that endogenous GLP-2 is dispensable for the regulation of lipid homeostasis under normal condition but it seems to play a beneficial role in pathological condition such obesity and type 2 diabetes, because chronic treatment with GLP-2 (3-33), a GLP-2R antagonist, increases dyslipidaemia and hepatic lipid accumulation only in high fat diet (HFD) fed mice [13].

GLP-2 inhibits gastrointestinal motility, and consequently it provides the opportunity to prolong the time available for digestion and absorption of nutrient [4,5,25,38,55,79]. The peptide modulation on the gastrointestinal motility may be due to central nervous mechanisms [38,47], but involvement of the enteric nervous system has been shown in studies using intestinal muscular strips *in vitro* [4,5,25]. Inhibition of gastric emptying has been related to GLP-2 anorixigen effects [14,38,55].

3.2. Food intake

Several experimental studies have suggested that GLP-2 can be considered as an anorexigen peptide, acting at central and/or peripheral level, in various animal species [14,38,42–44,52,72].

In fact, the GLP-2R have been localized in key regions of the brain for energy balance, including the hypothalamus, hippocampus and brainstem by different experimental approaches [53,76]. Although,