Abstract
Multiple peptide hormones produced within the gastrointestinal system also in the central nervous system aid in the regulation of energy homeostasis and metabolism. The list of these peptides is progressively increasing and includes glucagon-like peptide 2 (GLP-2) as an anorexigenic factor. GLP-2 is released from enteroendocrine L-cells following food intake and its principal target is represented by the gastrointestinal tract. GLP-2 has been shown to be an important intestinotrophic factor that stimulates epithelial cell proliferation and inhibits apoptosis. GLP-2 increases intestinal blood flow and the activity and expression of epithelial brush-border digestive enzymes and nutrient transporters, and consequently increases the intestinal digestive and absorptive capacity. It inhibits gastric and intestinal motility, thus providing another mechanism to increase absorption of nutrients. Current research has focused on determining its physiological actions and its biological mechanisms in the gut, while very little is known on the GLP-2 actions within the brain. This review provides an overview of the state of the art on GLP-2 biology.

Introduction
In the last decades a wealth of data has expanded our knowledge on the glucagon-like peptide 2 (GLP-2) as an important molecule involved in a wide variety of functions. GLP-2 was first discovered as an intestinotrophic factor in 1996, but today it is recognized as a pleiotropic hormone that exerts different actions, not only in the gastrointestinal tract but also in the central nervous system. Since the biological actions of GLP-2 converge at multiple levels on the regulation of nutrient assimilation and energy homeostasis, a great deal of interest has been generated for drug development with therapeutic potential. The aim of this review is to explore recent advances in our understanding of GLP-2 biology.

Synthesis, secretion and degradation
GLP-2 is a 33-amino-acid peptide, which is derived from the cleavage of proglucagon, a large prohormone that is mainly expressed in cells of the endocrine pancreas, in the enteroendocrine L-cells, most of which are located in the distal ileum and colon, in the brain. Alternative splicing of proglucagon through prohormone convertases leads to the tissue-specific release of GLP-2 and other peptides with diverse biological properties. In particular, in pancreatic alpha-cells proglucagon is cleaved by prohormone convertase (PC)-2 to form glucagon, the major glucagon fragment and intervening peptide (IP)-1. In the gastrointestinal tract and in the brain, processing of proglucagon, which is operated by PC1/3, results in glucagon-like peptide-1 (GLP-1), GLP-2, IP2, oxyntomodulin and glicentin. GLP-2 is released in response to stimulation by luminal nutrient, including glucose, fatty acids and dietary fiber.

After ingestion of nutrients, plasma levels of GLP-2 increase 2- to 5-fold, depending upon the size and nutrient composition of the meal. It has been supposed that the peptide diffuses across the subepithelial lamina propria to activate afferent nerves and/or to enter the circulation, thus it may act also as paracrine agent besides as endocrine hormone.
GLP-2 structure is highly conserved across different mammalian species. It contains an alanine residue at position 2, rendering it ideal substrate for cleavage and inactivation by the enzyme dipeptidyl peptidase 4 (DPP-IV) and resulting in the generation of inactive GLP-2. The degradation by DDP-IV has important consequences. First of all, the half life of intravenous GLP-2 is very short, about 7 min in healthy humans and secondly, use of DPP-IV inhibitors or the substitution of alanine with glycine as teduglutide avoids degradation and confers greater biological activity.

GLP-2 receptor

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. GLP-2R expression is restricted to the gastrointestinal tract and central nervous system, with limited expression in lung, cervix, and vagal afferents. Multiple experimental approaches have localized the GLP-2R to regions within the rodent central nervous system (CNS) including the hippocampus, hypothalamus and nucleus of the solitary tract in the mouse. The exact cellular localization of the GLP-2R in the gut has been a source of controversy which is probably derived from methodological problems or species-specific expression. GLP-2R may be present in enteroendocrine cells, enteric neurons and subepithelial myofibroblasts, but in murine gastrointestinal tract GLP-2R is expressed exclusively in neurons and myofibroblasts, and it is not present at mucosal level.

In mouse, GLP-2R-mRNA has been demonstrated with high levels of expression in the bowel and recently GLP-2R protein has been demonstrated throughout the gastrointestinal tract, with higher expression in gastric fundus and colon. The relative high prevalence of the GLP-2R in the gut might explain why, to date, GLP-2-mediated effects have been observed almost exclusively in the GI tract.

Actions of GLP-2 within the gastrointestinal tract

The main biological effects of GLP-2 are related to the regulation of energy absorption and maintenance of mucosal morphology, function, and integrity. Central to the beneficial effects of GLP-2 on the gut is its biological action to increase intestinal growth, due to the enhancement of crypt cell proliferation and inhibition of apoptosis, resulting in expansion of villous height. In fact, a large number of studies have demonstrated that exogenously-administered GLP-2 is tropic for the small intestine and, to a lesser extent, the colon. However, endogenous GLP-2 plays a role in the adaptative intestinal growth that occurs in rodents in response to oral re-feeding after a period of nutrient deprivation, as shown by using GLP-2 or GLP-2R knock out mice. The association between GLP-2 and intestinal growth/adaptation is most evident in a variety of pathological conditions, including post-resection intestinal adaptation, celiac disease, parenteral nutrition-induced intestinal atrophy and inflammatory bowel disease.

GLP-2 is able to maintain mucosal integrity by enhancing intestinal barrier function and decreasing transcellular and paracellular epithelial permeability. The ability of GLP-2 to increase barrier function has been confirmed in non-obese diabetic and ob/ob obese murine models. In fact, administration of a prebiotic to ob/ob mice induces GLP-2-dependent up-regulation of the tight junction proteins, zonula-1 and occludin. In addition, GLP-2 acts in pathophysiological states as an anti-inflammatory agent, reducing intestinal mucosal inflammatory cytokine production.

GLP-2 exerts numerous other actions within the GI tract to promote energy absorption. It increases the uptake of luminal nutrients, including sugars and lipids, by augmenting the activity and the expression of nutrient transporters and the expression of different enzymes involved in digestion. GLP-2 is able also to increase the mesenteric blood flow. GLP-2 has also been shown to inhibit gastric acid hypersecretion and the intestinal chloride secretion.
nutrient. Specifically, GLP-2 reduces the vagally-induced antral motility in pigs and it decreases the mouse gastric fundic tone leading to an increase of stomach capacity. Although it is not clearly established if the GLP-2 effect on mouse gastric stomach is physiological or pharmacological, the GLP-2 action on gastric fundus seems particularly interesting, because it could represent a safety signaling which well fits with the finding that GLP-2 is a chemical mediator inhibiting rodent feeding behavior. In fact, increase in the gastric volume might mean activation of stretch receptors and greater satiety signals to the brain, but electrophysiological experiments in vivo are necessary to confirm this hypothesis.

In mouse GLP-2 inhibits the intestinal transit in vivo and it reduces spontaneous or electrically-evoked cholinergic contractions of the small and large intestine in vitro. The peptide modulation on the gastrointestinal motility may be due to central nervous mechanisms, but involvement of the enteric nervous system has been also clearly shown through the in vivo studies. As GLP-2R is expressed in the subepithelial myofibroblasts and enteric nervous system as well as human enteroendocrine cells, it has been proposed that the peptide exerts its actions indirectly via downstream mediators deriving from GLP-2R-expressing cells. Indeed, neural VIP, nitric oxide and reduction of the acetylcholine release from enteric nerves have been reported to be involved in the inhibitory motor effects induced by GLP-2 in different regions of the mouse GI tract. However determining how GLP-2 produces its biological effects, which mediators are involved and how these mediators interact is an area of intense research and the reader is referred to a recent paper for a more detailed overview.

Extraintestinal actions of GLP-2
GLP-2 may be considered an anorexigenic peptide because intracerebroventricular administrations of GLP-2 reduce the food intake in rodents. Interestingly, in rats the anorectic response to GLP-2 seems to depend on a certain tone of central GLP-1 receptors because pharmacological antagonism of GLP-1 receptors by prior administration of exendin9-39 abolishes GLP-2 induced anorexia. On the contrary studies in mice have pointed to the opposite: Blocking central GLP-1 receptors with exendin-9 increases GLP-2 induced anorexia. Further studies focusing on the role of central GLP-2 receptors in appetite regulation are clearly needed. On the other hand, multiple experimental approaches have localized the GLP-2R to regions within the rodent CNS including the hypothalamus and hippocampus. Activation of the GLP-2R in the hypothalamus may be responsible for the effects of central GLP-2 administration on feeding behavior and because the hippocampus is sensitive to hunger and satiety signals, might influence appetitive behavior through inhibitory learning and memory process. However, up to date studies in humans have not demonstrated decrease in the food intake after peripheral GLP-2 administration, even if recent data have shown that intraperitoneal injections of teduglutide reduce food intake in mouse, suggesting a role for GLP-2 in the short-term regulation of the ingestive behaviour.

In general, very few studies have been conducted to elucidate the roles of the GLP-2 in the central nervous system. Consistent with a general cytoprotective effect of GLP-2 within the GI mucosa, the few studies have suggested that activation of GLP-2 receptors can protect neurons from excitotoxic damage. More specifically, GLP-2 has been reported to reduce glutamate-induced cell death in cultured hippocampal cells and to stimulate the proliferation of rat astrocytes. Antidepressant-like effects of GLP-2 that occur via monoamine pathways have also been noted in mice, but this has yet to be confirmed.

Conclusions and future directions
All the actions described make GLP-2 an attractive drug for the treatment or prevention of gastrointestinal disease in human subjects. However, because very few studies have been conducted to elucidate the roles of this peptide in central nervous system, we are still far from having an in depth understanding of the complex neurobiology of GLP-2. Therefore, future research efforts should aim at providing new information on the roles subserved by GLP-2 within the brain.