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Diverse roles of leptin in the gastrointestinal tract: Modulation of motility, absorption, growth, and inflammation

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Abstract

Objective—Leptin was discovered in 1994 as a hormone produced by adipose tissue with a modulatory effect on feeding behavior and weight control. Recently, the stomach has been identified as an important source of leptin and growing evidence has shown diverse functions for leptin in the gastrointestinal tract.

Methods—Using leptin as a keyword in PubMed, more than 17 000 articles were identified, of which more than 500 articles were related to the role of leptin in the gastrointestinal tract. Available abstracts were reviewed and more than 200 original articles were reviewed in detail.

Results—The available literature demonstrated that leptin can modulate several important functions of the gastrointestinal tract. Leptin interacts with the vagus nerve and cholecystokinin to delay gastric emptying and has a complex effect on motility of the small bowel. Leptin modulates absorption of macronutrients in the gastrointestinal tract differentially in physiologic and pathologic states. In physiologic states, exogenous leptin has been shown to decrease carbohydrate absorption and to increase the absorption of small peptides by the PepT1 di-/tripeptide transporter. In certain pathologic states, leptin has been shown to increase absorption of carbohydrates, proteins, and fat. Leptin has been shown to be upregulated in the colonic mucosa in patients with inflammatory bowel disease. Leptin stimulates gut mucosal cell proliferation and inhibits apoptosis. These functions have led to speculation about the role of leptin in tumorigenesis in the gastrointestinal tract, which is complicated by the multiple immunoregulatory effects of leptin.

Conclusion—Leptin is an important modulator of major aspects of gastrointestinal tract functions, independent of its more well-described roles in appetite regulation and obesity.

Keywords

Colon; Inflammation; Intestine; Leptin; Motility; Nutrient absorption

Leptin physiology and signaling

Leptin is a protein hormone that is a major product of adipose tissue and has well-described roles in the regulation of appetite and metabolism [1,2]. Although leptin was first discovered in adipose tissue, it is also produced in other organs including the stomach, skeletal muscle,
and pituitary gland [3,4]. Leptin is a product of the obese (ob) gene, which is located on chromosome 7 in humans and acts through its receptor OB-R. The stomach is the major source of leptin in the gastrointestinal (GI) tract. Endocrine and exocrine cells in gastric mucosa produce leptin; however, exocrine cells play a larger role [5,6]. Endocrine secretion of leptin occurs in various physiologic states, including fasting or refeeding after fasting. It has been shown that during these conditions the concentration of leptin increases in the serum and gastric mucosa [7]. Leptin and the soluble isoform of its receptor are secreted by chief cells in the gastric mucosa and remain stable in the acidic environment of the stomach and reach the duodenum in two forms: protein-bound and free [5]. Leptin receptors are abundant in the GI system, especially in the proximal part of the intestine. These receptors can be found on the luminal and basolateral borders of intestinal cells [8].

There are several OB-R isoforms as a result of the splicing of a single gene transcript [9]. Extracellular domain, transmembrane domain, and the first 29 amino acids of the cytoplasmic domain are identical in all isoforms of leptin receptors. According to the length of the intracellular domain, there is one long isoform (OB-Rb) and four short isoforms (OB-Ra, c, d, f), which differ in their cytosolic carboxy terminals. There is one soluble isoform (OB-Re) that lacks the transmembrane domain and may be involved in leptin transport in the blood [10]. It has been suggested that this type of receptor can indirectly regulate the bioactivity of leptin through modification of the leptin-to-soluble leptin receptor ratio [11]. It has recently been reported that the soluble leptin receptor, when coadministered with leptin, centrally or peripherally decreases the phosphorylation of signal transducer and activator of transcription-3 (STAT-3) and blocks the regulatory effects of leptin on food intake and weight [12]. When leptin binds to the OB-Rb receptor, it activates the Janus kinase/STAT pathway and it activates the mitogen-activated protein kinase signal transduction pathways when attached to short isoforms (OB-Ra, c, d, f) [13]. Janus kinase/STAT activation leads to the phosphorylation of tyrosine residues of leptin receptors at three different sites. Each of the three tyrosine phosphorylation sites recruits specific downstream signaling proteins. One recruits tyrosine phosphatase Src homology-2 domain-containing tyrosine phosphatase-2, which induces extracellular signal-regulated kinases (ERK)-1/2 and suppresses cytokine signaling-3. Another phosphorylation site leads to the activation of STAT-5, and STAT-3 is another downstream signaling pathway activated by leptin receptors [14]. These downstream pathways have been shown to be involved in effects of leptin on various tissues. For example, STAT-3 mediates the effect of leptin on food intake, hepatic glucose production, and gonadotropin secretion [15], whereas control of lipogenesis in adipose tissue, induction of arterial intima formation by leptin, increase of absorption of peptides, and proinflammatory effects of leptin in the colon and liver have been suggested to be independent of STAT-3 [16].

**Effect of leptin on GI tract motility**

Leptin has complex effects on motility of the GI system. Afferent and efferent vagus nerve endings contain leptin receptors [17]. In rat stomach, two groups of vagal afferent nerve endings based on their sensitivity to leptin and their effect on motility have been identified; one is leptin-responsive and produces a stimulatory response to leptin; the second group is usually leptin-insensitive and produces an inhibitory response to leptin [18]. In the small intestine, leptin can cause excitatory and inhibitory effects on mechanoreceptors and thus has a complex effect on intestinal motility. It has been shown that leptin deficiency increases the rate of gastric emptying [19], increases transit activity in the jejunum, and shortens total transit time in the small intestine [20]. In addition, some studies have shown that central administration of leptin delays gastric emptying [21]. Recently, the fasting plasma level of leptin was positively correlated with myoelectrical abnormalities in the stomach associated with delayed gastric emptying in diabetic patients [22].
The leptin-induced inhibition of food intake and the stimulation of pancreatic exocrine secretions can be blocked by a cholecystokinin-1 (CCK-1) receptor antagonist [23]. One in vitro study showed that STC-1 cells that secrete CCK have leptin receptors and are stimulated by the presence of leptin. Duodenal delivery of leptin in vivo increases the concentration of CCK in the serum. Feeding decreases the amount of leptin in the gastric juice and increases the amount of leptin in the duodenum even in leptin receptor-deficient mice; however, a surge of serum CCK after feeding is not observed in such mice [24]. CCK itself increases the release of leptin from gastric glands, suggesting that leptin and CCK comprise a positive feedback loop. Locally injected intra-arterial leptin stimulated motility in the small intestine in cats pretreated with CCK, whereas leptin alone did not induce such activity [24,25]. This suggests that modulation of vagal fibers in the presence of CCK plays a key role in the observed effects of leptin on intestinal motility. Gaigé et al. [25] also suggested that, depending on the absence or presence of CCK, leptin can switch its regulatory role between feeding behavior and motility. Leptin, in the absence of CCK, regulates the feeding behavior and appetite by exciting type 1 vagal nerves and inhibiting type 2 vagal nerves while in the presence of CCK, enhancing the motility of the GI tract.

**Effect of leptin on nutrient absorption**

Available data suggest that leptin has complex effects on macronutrient absorption in physiologic and pathologic states. In physiologic states, leptin has been shown to decrease carbohydrate absorption by inhibiting $\alpha$-glucose transport in the preprandial state and to upregulate glucose absorption in the postprandial state. Sodium–glucose transporter-1 is expressed in small and large intestinal mucosa and is responsible for absorption of glucose. Luminal and systemic administrations of leptin decrease the activity of this cotransporter through various mechanisms. It has been suggested that luminal leptin, most likely produced by gastric mucosa, rapidly decreases the expression and activity of sodium–glucose transporter-1 through a direct effect at the brush border, whereas systemic leptin has a slower indirect effect that is at least in part mediated by CCK [26]. Sodium–glucose transporter-1 is the major transporter of glucose during the preprandial state. In the postprandial state, glucose transporter (GLUT)-5 and GLUT-2 become upregulated and their activity increases. Recently, it has been reported that luminal leptin increases the activity of GLUT-2 and GLUT-5 transports through the activation of protein kinase C and adenosin mono phosphate activated protein kinase (AMPK)-$\alpha$, whereas oral fructose rapidly induces the release of leptin in the GI lumen without significantly affecting plasma leptin levels [27]. This observation suggests that in preprandial state leptin produced by gastric cells decreases the absorption of glucose, whereas in the postprandial state leptin has an important role in increasing the uptake of glucose.

Leptin has also been shown to increase the absorption of small peptide products of protein digestion through the di-/tripeptide transporter PepT1 [28]. Leptin produced from gastric mucosa and present in the proximal small bowel lumen appears to recruit an intracellular pool of PepT1 to be expressed on the brush border of intestinal cells [28]. In the long term, leptin appears to increase the translation and mRNA production of PepT1 in the small intestine [29,30]. However, in diet-induced obesity in mice (a chronic hyperleptinemia state), leptin receptors are downregulated, which in turn leads to a decrease in small intestinal expression of PepT1 and absorption of small peptides [31]. This effect of leptin is independent of STAT-3 or STAT-5 and is modulated by the ERK-1/2 pathway [31]. Leptin-deficient mice have significantly decreased PepT1 expression and activity, which is reversible by peripheral administration of leptin. In such mice, activities of the jejunal aminopeptidase and dipeptidyl peptidase are also decreased compared with wild-type mice [32]. Because PepT1 has an important role in absorption of nutrients, as well as several
drugs, a better understanding of the role of leptin in the regulation of this peptide transporter may have important clinical applications.

Intravenous infusion of leptin decreases apolipoprotein A-IV, whose synthesis is stimulated by fat absorption [33]. Leptin administered to the basolateral side of Caco-2 cells was found to inhibit the secretion of triacylglycerols, the biosynthesis of apolipoproteins B-100 and B-48, and the output of chylomicron and low-density lipoproteins [34]. In the same cells, luminal leptin can increase the intracellular pool of proton-linked monocarboxylate transporter-1 and its translocation to the luminal membrane and, in consequence, increases the uptake of butyrate by colonic cells [34]. Butyrate is a short-chain fatty acid produced by microbial fermentation of carbohydrate, which is a main source of energy in intestinal cells and has important anti-inflammatory and cell regulatory functions. Leptin also has been shown to increase the expression of liver and intestinal fatty acid-binding proteins in vitro, which might participate in the uptake, intracellular metabolism, and transport of long-chain fatty acids [35].

In a mouse model of short bowel syndrome after massive small bowel resection, exogenous leptin administration increased the absorption of sucrose [32]. Leptin also increases the expression and activity of GLUT-5, which is a glucose and galactose transporter in enterocytes after partial small bowel resection [36]. After bowel resection, leptin administration induces differential effects on carboxy- and aminopeptidases in the ileum, increasing the activity of aminopeptidase and decreasing the activity of carboxypeptidase. Exogenous leptin also was shown to increase the intestinal absorption of fat in this model of short bowel syndrome [32]. Although data are very limited in humans, one study failed to find any significant difference between serum levels of leptin in patients with short bowel syndrome after massive small bowel resection and unrected controls, regardless of the route of nutrition (i.e., parenteral versus oral as the primary route of feeding) [37].

**Leptin as a trophic factor in the GI tract**

Although there is some evidence in the literature suggesting that leptin does not stimulate growth in the GI tract mucosa, several studies have shown that leptin acts as a trophic factor in the GI tract and can stimulate gut epithelial cell proliferation when given exogenously [38,39]. In neonatal piglets, leptin has been shown to have a stimulatory effect on the development of intestinal mucosal morphometry, proliferation of mucosal epithelial cells, enzymatic activity in the brush border of enterocytes, and, as outlined earlier, in nutrient absorption [40]. After massive small bowel resection, the leptin receptor gene and protein expression were upregulated in residual jejunal and ileal mucosa, concomitant with adaptively increased villus and crypt growth [41,42]. Treatment with exogenous leptin enhanced all of these effects [41,42]. Leptin-deficient ob/ob mice demonstrated decreased cellular proliferation and increased apoptosis in intestinal cells after massive small bowel resection [43]. This study and a study reported by Lin et al. [44] suggested that leptin increases apoptosis in intestinal cells, in contrast to the decrease in apoptosis observed by other investigators [42].

The mitogenic and antiapoptotic effects of leptin make it a potential tumorigenic factor. The association between a high-fat diet and obesity with colon cancer and the association between a high-fat diet and high concentrations of leptin in the serum were suggestive of a role for leptin in colon carcinogenesis [45]. However, experimental data have been controversial and there is no conclusive evidence, to date, for the role of leptin in carcinogenesis in colorectal cancer. It has been suggested that leptin and its receptor are expressed in cancer tissues and that leptin may promote cancer progression in an autocrine and paracrine manner. Leptin can stimulate mitogen-activated protein kinase activity in vitro.
and increase the proliferation of gastric mucosa cell lines [46]. Leptin also induces cell proliferation and migration in normal and malignant colorectal cells [39, 47]. Leptin expression has been found in gastric adenocarcinoma, colorectal polyps, and adenocarcinoma of the colon [46, 48, 49]. An association between high leptin concentration and increased risk of Barret’s esophagus and squamous cell carcinoma of the esophagus has been reported [50]. Leptin may accelerate fibrosis in the setting of chronic liver injury [51] and might precipitate fatty changes in non-alcoholic liver disease [52]. Outside the GI tract, leptin expression has been reported to be upregulated in breast carcinomas [53]. Although some studies have reported that high levels of leptin in the serum correlate with increased proliferation of colonic cells [48] or the risk of cancer in rats consuming a high-fat diet [45], other studies have not shown a significant difference in the concentration of leptin in the serum of patients with colorectal cancers compared with normal controls [45]. Some studies have even showed lower levels serum leptin in patients with advanced cancer, but the role of food intake was unclear in such observational studies [54]. In rats, leptin decreased the precancerous colonic mucosal lesions induced by azoxymethane [55]. Expression of leptin was found to be increased in human colorectal carcinomas and even in the normal colonic mucosa adjacent to the tumors [49]. The investigators also showed that the level of leptin expression correlated with the degree of differentiation of the tumor, with poorly differentiated tumors expressing less leptin [49]. Transgenic mice lacking leptin receptors were shown to be prone to azoxymethane-induced premalignant lesions in colonic mucosa [56]. Moreover, this picture has become more complex after studies indicating that leptin might have a role in the regulation of the antitumor immune response in colonic cells [57, 58]. On the one hand, leptin induces colonic cell proliferation and has antiapoptotic effects; on the other hand, leptin has been shown to enhance antitumor immune responses, suggesting that the observed increase in expression of leptin receptors in tumor cells might be a homeostatic response.

Leptin and immune function and gut mucosal inflammation and injury

Leptin has important modulatory effects on the immune system. Congenital leptin deficiency increases the incidence of infection-related death during childhood [59]. Leptin modifies the cytokine production pattern toward a type 1 T-cell helper response by promoting the release of interleukin (IL)-2 and interferon and inhibiting IL-4 secretion, reverses starvation-induced immunosuppression [60], and directly stimulates the expression and release of IL-1 and tumor necrosis factor-α by T cells [61]. In addition, leptin facilitates type 1 T-cell helper responses by promoting the differentiation of antigen-presenting dendritic cells [62]. However, leptin has also been shown to exhibit anti-inflammatory properties by stimulating the expression and production of the IL-1 receptor antagonist in human monocytes [63]. Leptin receptor-deficient mice exhibit impaired natural killer cell activity and leptin has been shown to enhance the proliferation and cytotoxicity of natural killer cells [64] and protect them from apoptosis [65]. Leptin induces the production of nitric oxide and proinflammatory cytokines in macrophages and monocytes [66] and enhances the release of reactive oxygen by neutrophils [67]. Leptin deficiency results in an attenuated adaptive immune-mediated response and causes inadequate control of inflammation [59].

Leptin modulates inflammatory and anti-inflammatory responses in the GI tract. Acute administration of leptin stimulates the production and secretion of corticotropin [68]. Conversely, chronic exogenous leptin can inhibit production of corticotropin-releasing hormone and corticotropin, block the physiologic surge of corticosteroids in response to stress, and decrease the production of glucocorticoids by the adrenal glands [69]. Therefore, at the systemic level, acute exogenous administration of leptin was shown to prevent experimental induced colitis, an effect that has been shown to be reversed by blockage of corticosteroids receptors [70]. Leptin might prevent gastric ulcer formation by increasing the
activities of the cyclooxygenase and nitric oxide pathways and by enhancing mucus secretion [71]. Serum leptin concentrations are increased in experimental animals with intestinal inflammation and human patients with inflammatory bowel disease [72]. It has been suggested that inflammation-induced anorexia is the major reason for hyperleptinemia and it was shown that leptin levels correlated with the level of inflammation and anorexia [73]. Others have reported that serum concentrations of leptin decrease in patients with Crohn’s disease, whereas treatment with infliximab (tumor necrosis factor-α inhibitor) had the opposite effect [74,75].

It has also been suggested that leptin may play a role in the inflammatory process in the colon. Leptin-deficient mice are resistant to acute and chronic intestinal inflammations induced by chemical agents [76]. Levels of proinflammatory cytokines and neutrophil infiltration into the colonic tissue are significantly suppressed in leptin-deficient mice compared with wild mice, and these effects are reversible by the administration of leptin [76]. Leptin-deficient mice are also resistant to type 2 helper T-cell–mediated chemically induced colitis, and this resistance is reversible by leptin administration [58]. The human [h] PepT1 is suggested to have a role in inflammatory bowel disease by transport of bacterially derived proinflammatory peptides [77,78]; leptin enhances hPepT1 promoter activity and increases hPepT1 mRNA and protein expression in the gut [17]. In patients with ulcerative colitis, inflamed colonic epithelial cells expressed larger amounts of leptin and released leptin into the intestinal lumen; this in turn induced epithelial wall damage and neutrophil infiltration [79]. Luminal leptin concentrations during inflammation in patients with inflammatory bowel disease are much higher than those observed in normal colonic luminal fluid [79], and leptin is overexpressed in creeping fat in patients with Crohn’s disease [80]. In contrast, Valentini et al. [81] did not find any significant increase in serum leptin levels in patients with inflammatory bowel disease or a correlation between inflammation or disease activity and serum levels of leptin. It has been suggested that leptin might produce proinflammatory effects in mice by the STAT-3 action pathway [76]. Increased levels of STAT-3 have been detected in mice after experimentally induced colitis and in colon samples of humans with Crohn’s disease or ulcerative colitis [82]. Luminal leptin was shown to activate mucin-secreting goblet cells in the colon and stimulate expression of secreted and membrane-bound mucin [83,84]. Because mucin is an important part of the colonic defense mechanism and protects epithelial cells from physical, microbial, and chemical injuries, leptin secretion during intestinal inflammation may represent an adaptive beneficial response in this setting.

The role of leptin in ischemic injury and healing of the GI tract has also been studied. Leptin administration accelerated the healing of colonic anastomosis [85]. In an intestinal ischemic injury model in mice, exogenous leptin was shown to decrease the level of intestinal tissue injury [86]. Other studies have shown that leptin controls the production of nitric oxide by activating nitric oxide synthase in a dose-dependent manner in rats [87]. Nitric oxide has a vasodilatory effect and leptin was shown to relax the rat mesenteric artery through its effect on nitric oxide [88].

**Leptin and its interaction with ghrelin in the GI tract**

Ghrelin, first identified in 1999 as primarily produced in the stomach, is a 28-amino acid peptide and its receptor is a member of the growth hormone secretagogue receptor family. Ghrelin induces secretion of growth hormone from the pituitary gland in vivo and in vitro [89]. Fasting can increase expression and secretion of ghrelin, whereas refeeding decreases these [90,91]. Ghrelin-synthesizing cells are abundant in the GI tract, especially in the stomach [92,93].
Soon after its discovery, it was shown that ghrelin has a major role in regulating feeding behavior [90,91]. Effects of ghrelin on appetite and observed changes in ghrelin levels in response to fasting or eating are opposite those of leptin [94]. Ghrelin induces adiposity in adipose tissues [95], increases appetite [93], and initiates eating behavior [96]. Circadian changes in the level of circulating ghrelin and leptin are reciprocal [97]. Leptin and ghrelin also have contradictory effects on intestinal inflammation. For example, ghrelin has been shown to ameliorate inflammation in the GI tract in a mouse model of colitis [98]. Ghrelin’s effect on GI tract motility is also generally opposite that of leptin. Ghrelin stimulates gastric acid secretion and motility [99] and accelerates gastric emptying and small intestinal transit [100]. Leptin has been shown to decrease the expression and secretion of ghrelin from gastric mucosa [101]. Interestingly, leptin cells are adjacent to ghrelin cells in the gastric mucosa, surrounding ghrelin cells in the lower half of stomach, possibly providing a paracrine regulation of ghrelin secretion [94]. However, ghrelin shows some effects on the gut that are similar to those of leptin. For example, ghrelin decreases the rate of apoptosis in intestinal cells [102], ameliorates ischemic–reperfusion injury [103], and decreases the permeability of the intestine in case of shock (partly by increasing mucin secretion) [104]. Further studies are required to completely elucidate the nature of the interaction between ghrelin and leptin in health and disease.

Summary

Leptin has multiple complex roles in the GI tract (Fig.1). It was initially described as a promoter of satiety and a regulator of food intake. However, the mechanism of leptin’s effect on satiety and the complexity of the interactions among leptin, other recently discovered appetite regulatory polypeptides, and pancreatic exocrine hormones (CCK, etc.) continue to be explored and may ultimately provide insight into obesity and appetite. Motility of the GI tract may be one aspect in which leptin induces satiety. Furthermore, leptin clearly has a role in nutrient absorption, which may differ in the physiologic and pathologic disease states. Leptin’s complex role in GI motility and nutrient absorption is a key to understanding the role of leptin in linking nutritional status, obesity, and metabolism. Recent data about interaction between leptin and neuropeptide Y in the regulation of absorption might help to elucidate this role [105,106].

Leptin also has significant effects as a local trophic factor in the GI tract and as an immune system modulator. These effects not only suggest a role in GI cancers but also inflammatory bowel disease and likely other autoimmune diseases. Gastric production of leptin contributes to trophic control of GI cells, but it is unknown whether gastric production of leptin has significant effects on the GI immune system. Clearly, leptin itself alters the innate and adaptive systemic immune response and may participate in diseases of the intestine and colon systemically or even locally.

In this review, we highlight the GI effects of leptin and its relation to GI motility, nutrient absorption, trophic effects on GI cells, and the immune system. The future directions in the study of leptin are broad and specifically should be focused on the interplay between leptin and other polypeptides in the regulation of motility, absorption, and satiety to better understand the effects of leptin on nutritional status and metabolism, which are major contributors to obesity. Furthermore, trophic effects in the GI tract and immune system modulation effects of leptin can provide insight into GI cancers and inflammatory disorders of the GI tract including Crohn’s disease and ulcerative colitis. Ultimately, the many effects of leptin are only beginning to be understood and the effects on the GI tract likely affect many pathologic states including obesity, GI cancers, and inflammatory bowel disease.
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Fig. 1.
Effects of leptin on the gastrointestinal tract. Leptin, produced by adipose tissue and gastric mucosa, modulates numerous aspects of gastrointestinal function. Leptin, mainly produced by the gastric mucosa, regulates motility of the stomach and small intestine through its interaction with CCK and the vagus nerve. Leptin can act as a proinflammatory cytokine in colonic IBD. Leptin influences macronutrient transport in the small intestine in part by its action to regulate PepT1 and SGLT-1 transports of di-/tripeptides and glucose, respectively. Leptin exerts proliferative and antiapoptotic effects, suggesting that leptin is a potential tumorigenic factor. Several immunoregulatory effects relevant to colon cancer have been attributed to leptin. CCK, cholecystokinin; IBD, inflammatory bowel disease; SBS, short bowel syndrome; SGLT-1, sodium–glucose transporter-1.