

Leptin, gut, and food intake

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Abstract

Hyperphagia (overeating) is often associated with energy over-storage and obesity, which may lead to a myriad of serious health problems, including heart disease, hypertension, and type 2 diabetes. Thus, understanding the complex pathological mechanisms underlying hyperphagia and obesity has an important clinical significance. Leptin, or ob protein, is a key element in the long-term regulation of food intake and body weight homeostasis. It circulates in the blood at levels correlated with body fat mass. Leptin binds to specific receptors in the hypothalamus to mediate events that regulate feeding behavior. In light of new evidence, the initial view that leptin is an adipocyte-derived signal, which acts centrally to decrease body weight, has been modified. It has been shown that leptin may also have specific functions in the gastrointestinal tract, suggesting that feeding and energy homeostasis is regulated by both central and peripheral signals. Evidence supports the view that leptin integrates short-term, meal-related signals from the gut into long-term regulation of energy balance. In addition, the gastric leptin level is altered by the nutritional state and the administration of cholecystokinin. This commentary aims to review the evidence of the role of leptin as a peripherally acting signal in the gut in the regulation of nutrient intake, adiposity, and body weight. Based on currently available data, some potential future studies are suggested. © 2002 Elsevier Science Inc. All rights reserved.

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1. Central and peripheral effects of leptin

Leptin, the product of the *ob* gene, was first identified as a hormone secreted by adipose tissue. It regulates feeding behavior and energy balance. It was recognized as an adipostatic signal which, when injected into rodents with genetic [1–5] or diet-induced [1] obesity, decreased body weight and adiposity, and improved metabolic control by regulating central and peripheral effector pathways. A deficiency of leptin in mice [6] and human subjects [7] is associated with massive obesity. Chronic administration of leptin to animals, or overexpression of leptin in transgenic mice [8], reduces body fat by reducing food intake and increasing the catabolic activity of the sympathetic nervous system. Paradoxically, most obese humans and mammals with diet-induced obesity have high leptin levels [9]. The popular view that leptin is an anti-obesity modulator has to

be reconciled with the failure of high endogenous leptin levels in humans and other mammals to prevent obesity [10]. Apparently, a state of leptin resistance exists in obese humans. Thus, a simple exogenous leptin therapy is insufficient in treating human obesity.

Leptin is secreted primarily from white adipose tissue, and its levels in circulation are correlated with the degree of adiposity [11]. Circulating leptin gains access to the brain via a receptor-mediated transport system [12], and acts on the long form of the leptin receptor in the medial hypothalamus. The interaction of leptin with hypothalamic receptors influences two peptide systems, pro-opiomelanocortin and neuropeptide Y, which mediate the effects of food intake in the CNS by regulating long-term feeding behavior and energy balance [11,13,14]. Leptin is cleared mainly by the kidneys, and, thus, patients with end-stage renal disease have elevated leptin levels [15].

In light of new evidence, the initial view that leptin is an adipocyte-derived signal, which acts centrally on hypothalamic targets to decrease body weight, has been modified. It is now recognized that leptin is also secreted from the gastric mucosa [16–18], and functions directly from the gut. The hypothesis that gastric leptin is a peripherally

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Abbreviations: NTS, nucleus tractus solitarius; CCK, cholecystokinin; JAK, Janus kinase; STAT, signal transducer and activator of transcription; PVN, paraventricular nucleus.

acting signal, which acts directly on the gut and modifies gut afferent signals to the central neural networks, is particularly interesting. Using electrophysiological techniques on a rat stomach–brainstem model, it was observed that gastric leptin increased the activity of NTS neurons in the caudal brainstem, the first relay station for gastric vagal afferents [19]. It has also been demonstrated that leptin potentiates the activity of CCK-responsive vagal afferents [20] and NTS neurons [21] and inhibits the activity of galanin-responsive NTS neurons [22]. *In vivo* studies show a synergistic effect between i.p. leptin and CCK to suppress food intake and body weight in lean mice [23]. In addition, i.p. leptin also reduces body weight gain in neonatal rats [24]. These observations suggest that leptin may have a physiological role in the gut. The following sections review the evidence of the role of leptin as a peripherally acting signal in the gut in the regulation of body weight and adiposity.

2. Presence of leptin in the gut

Recent evidence supports the view that in humans and rats, leptin is secreted not only from the placenta and adipose tissues, but also from the gut. Leptin mRNA and leptin protein have been detected in the chief cells of human stomach mucosa [17,18] and rat gastric fundic mucosa [16]. It is recognized that leptin levels in the stomach are altered by the nutritional state and the administration of CCK. Moreover, the synthesis and secretion of gastric leptin involve a 19K leptin precursor, which is not involved in adipocyte-secreted leptin [16]. Under postprandial conditions, leptin immunostaining was lower than during fasted conditions [17]. In the rat, gastric leptin was decreased slightly by starvation, but was not significantly different from the fasted state [16]. Refeeding of fasted rats led to a 66% decrease in gastric leptin after 15 min and a small increase in plasma leptin. A similar pattern of leptin secretion was seen after the i.p. administration of CCK to fasted rats. However, CCK was not a stimulus for leptin release from isolated adipocytes [16].

Under the stimulation of secretin and pentagastrin, leptin levels increase in gastric juice where it is detected free and stable. Leptin has also been detected in the endocrine cells of the stomach. Secretory granules of P cells in the basal portions of glands were immunoreactive for leptin [17]. It is hypothesized that the increase in circulatory leptin observed after the stimulation of pentagastrin or secretin is due to release from this endocrine source. The leptin receptor (Ob-R) was first isolated from the mouse choroid plexus by an expression cloning strategy [25]. Of the five Ob-Rs subsequently identified, only Ob-Rb (the long receptor isoform) contains intracellular motifs required for activation of the JAK-STAT signal transduction pathway [26,27]. Ob-Rb has been detected from the human fundic mucosa [18] and jejunum [28], suggesting that the gut is a direct target of gastric leptin.

3. Leptin action in the gut

Two different types of metabolic and/or hormonal signals are thought to operate in the regulation of body fat: long-term signals like insulin and leptin, and short-term signals of which CCK is the prototype. Previous groundbreaking studies reported that peripheral administration of leptin reduced food intake and body weight in lean and *ob/ob* mice [1–3]. Subsequent kinetic studies showed that the reduction in food intake induced by leptin was of slow onset. Cumulative food intake of 24-hr fasted lean mice was reduced only between 4 and 7 hr after i.p. injection of leptin [22,29]. In contrast, CCK administered i.p. induced a reduction in food intake after 15 min [30,31]. As a result, it was then hypothesized that the long-term adipocyte signal leptin may also act peripherally by increasing the efficacy of meal-related short-term signals, such as CCK. Indeed, coinjection i.p. of leptin and CCK into lean mice dose-dependently reduced food intake by 47–83% during the first hour, while neither CCK nor leptin injected alone was effective during the same period [23]. When leptin was injected i.p. into lean mice followed 3 hr later by a sub-threshold dose of CCK, the total daily food intake was more suppressed than after leptin alone [32]. It is also recognized that the CCK–leptin interaction to reduce food intake is mediated by the CCK-A receptor [29]. The results of these reports suggest that leptin and the CCKergic system interact to reduce food intake and body weight via peripheral pathways. The central administration of leptin has been reported to reduce food intake by specifically affecting meal size. The reduction in food intake in both male and female rats was accounted for by a decrease in meal size [33]. Further studies are necessary to determine whether the hypophagic effect of peripheral leptin and CCK is due to a reduction in meal size and/or meal frequency, and whether regulation of metabolic rate or thermogenesis is involved.

Leptin is engaged in other functions in the gut. It is involved in maintaining gastric epithelial cell integrity and gastroprotection. There is evidence that leptin secreted in the stomach protects the gastric mucosa against ethanol-induced damage by a NO-dependent mechanism [34]. *In vivo* studies have shown that leptin induces a proliferative response in gastric mucosal cells [35]. It is postulated that direct leptin signaling in the intestine may be involved in the regulation of nutrient absorption and intestinal motility. The functional Ob-Rb is predominantly expressed in the jejunum and weakly in the ileum, the two major sites involved in lipid handling [28]. Leptin administered i.p. to fat-loaded mice induced STAT5 DNA binding, and reduced apolipoprotein transcript levels in the jejunum [28].

It is recognized that food intake leads to changes in behavior. For example, leptin induces changes in feeding and exploratory behavior associated with food intake [36]. It may be an upstream factor in the mechanisms underlying these behaviors. In addition, leptin levels are high in patients with liver cirrhosis [37], suggesting that the liver

may be involved in leptin synthesis. Alternatively, the liver may also be involved in the degradation of leptin, hence inducing an increment of leptin levels when liver function is compromised. Several recent studies have shown that leptin regulates both the secretion and tissue responsiveness of insulin [38–40] and has potent anti-diabetic effects [41]. In hepatocytes, leptin has complex effects on the insulin response. It stimulates glucose transport and turnover consistent with an insulin-like response. However, it up-regulates gluconeogenesis, suggesting that leptin may contribute to hepatic insulin resistance [42].

4. Mechanisms of action of leptin in the gut

Vagal afferent fibers are the primary neuroanatomical link between the gastrointestinal tract and the central networks regulating food intake [43]. It is recognized that vagal afferents mediate the synergistic interaction between leptin and CCK to reduce food intake. Functional ablation of C-afferent fibers by systemic capsaicin abolished the leptin–CCK-induced reduction of food intake in mice [23]. Electrophysiological studies have shown that gastric vagal afferents are responsive to leptin. In addition to leptin secreted locally in the stomach, vagal afferents are also responsive to circulating leptin. In a stomach-gastric vagus-gastric artery preparation, intra-arterial administration of leptin increased gastric vagal afferent activity [20]. In the same study, afferent terminals were identified, which were only responsive to leptin after sensitization with CCK. There is evidence that hepatic vagal afferents are also responsive to leptin. Administration of leptin into the portal vein of rats resulted in a sustained increase in hepatic vagal afferent activity [44]. The results of these electrophysiological studies provide evidence for a peripheral gastric leptin action and its interaction with CCK, a short-term satiety signal, on vagal afferents.

The precise mechanism of how leptin and its interactions with CCK and other gut neuropeptides modulate vagal afferent activity remains to be determined. It is well known that CCK modulates vagal afferent activity via CCK-A receptors [45,46] located on vagal terminals [47]. The presence of a signaling-capable leptin receptor that can initiate the JAK-STAT signal transduction pathway on vagal afferents has yet to be determined. On the other hand, the rapid electrophysiological effects that have been reported [19–21] are not likely to involve STAT-mediated transcription. Alternatively, leptin could also potentiate intracellular signaling pathways activated by CCK [48], or activate vagal afferents secondary to leptin-induced changes in intragastric pressure.

Electrophysiological and neuroanatomic studies have identified CNS targets for the peripheral leptin–CCK interaction. The effects of gastric leptin on NTS units processing gastric vagal inputs have been evaluated [19]. The medial NTS is the first relay station for vagal

afferents that form the sensory limb of the gastrointestinal vago-vagal reflexes. Using a neonatal stomach–vagus–brainstem preparation, it has been observed that when applied to the stomach compartment of the preparation, leptin increased the activity of a population of NTS neurons in a concentration-dependent fashion [19]. In addition, compared with 1-day-old rats, 8-day-old rats showed both a higher percentage of activation responses and an increased level of activity of NTS neurons. These changes may reflect the maturation of leptin receptor expression and activity during development. In a subsequent study [21], it was demonstrated that the activity of leptin-responsive NTS neurons was increased by the application of CCK to the gastric compartment. Data from the same neonatal rat study showed that the distal stomach is responsible for the CCK-gastric effects on NTS neuronal activity.

In fasted mice who reduced their food intake after CCK and leptin were injected *i.p.*, Fos positive cells were selectively localized in the PVN of the hypothalamus [49]. It is interesting to note that the PVN is also a target of central-acting leptin [50]. In another study in which leptin was administered *i.c.v.* 1 hr before CCK, c-Fos induction was demonstrated in the NTS as well as in the PVN [51]. The implicit suggestion for the induction of c-Fos in the NTS by centrally acting leptin was the presence of a leptin-activated descending pathway from the PVN, altering NTS cell response to peripheral CCK. Conversely, from the NTS, ascending pathways may convey signals to the PVN and integrate to central-mediated leptin signals. Recently, Yuan *et al.* [22] demonstrated that galanin, an orexigenic peptide present in the stomach, decreases leptin-induced increases of NTS neuronal activity. It is recognized that galanin, acting in the CNS, regulates the expression of neuropeptide Y, also a CNS target of central-acting leptin [13]. Whether leptin may interact with gut signals other than CCK and galanin to regulate meal initiation has yet to be determined. Fig. 1 illustrates our current knowledge on the central and peripheral actions of leptin in modulating nutrient intake and energy homeostasis.

5. Summary and future work

Existing evidence supports the hypothesis that leptin plays a significant role in the digestive system. The chief cells of the human gastric fundic mucosa secrete leptin, and the signaling-competent Ob-Rb receptor is present in gastric epithelial cells [18] and jejunal epithelium of the rat [28]. Behavioral studies further support the theory that leptin in cooperation with CCK may control meal-size [23,32]. Leptin increases the activity of vagal afferents from the gut, the major afferent pathway for relaying digestive information to the CNS. Leptin administered to the gastric artery synergistically interacts with CCK to increase the firing frequency of gastric vagal terminals [23]. Leptin applied to the stomach increases the activity of

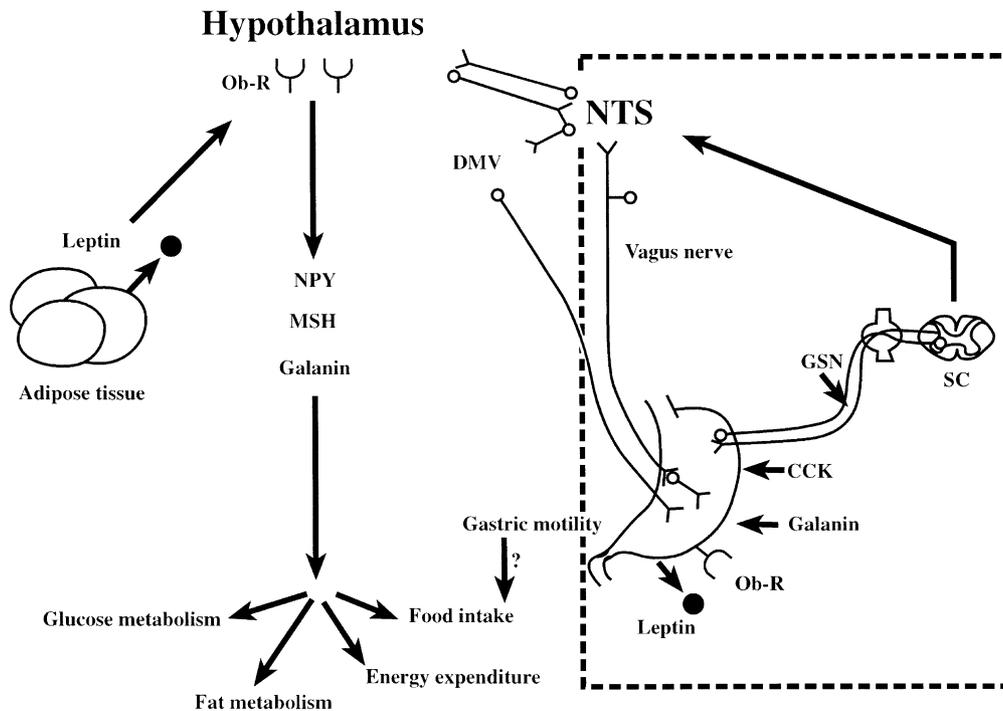


Fig. 1. Schematic diagram that summarizes the current knowledge on the central and peripheral actions of leptin in modulating nutrient intake and energy homeostasis. The role of leptin as a peripherally acting signal in the gut is shown in the dotted box. Key: (●), leptin; (⊂), Ob-R or leptin receptor; NPY, neuropeptide Y; MSH, melanocyte stimulating hormone; CCK, cholecystokinin; DMV, dorsal motor nucleus of vagus; NTS, nucleus tractus solitarius; SC, spinal cord; and GSN, greater splanchnic nerve.

a population of NTS neurons responsive to gastric vagal stimulation [19], and also potentiates CCK signaling via the vagus [21]. One of the major physiological roles of leptin in regulating food intake appears to occur in the gut.

Future studies should be directed to the precise mechanisms by which leptin interacts with CCK, the neural circuitry in the CNS beyond the brainstem, and the satiety factors involved. Likewise, the physiological significance of leptin's actions on jejunal epithelium, a major site of fat handling in the gut, needs to be determined. The question of whether the lack of leptin secretion or the resistance to leptin action in the gut can contribute to obesity and its related syndromes remains to be answered. Nevertheless, mounting evidence supports the view that leptin integrates short-term, meal-related signals from the gut into long-term regulation of energy balance.

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