A new role for leptin as a direct satiety signal from the stomach

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The prevalence of obesity and its secondary health risks have dramatically increased over the last two decades (17), and despite accelerated research and drug development by the pharmaceutical industry, no effective treatment is in sight (5). Although it is clear that sedentary lifestyle is one of the major culprits and that increased physical activity may be the best therapy to keep body weight in check, the control of food intake is equally important. Leptin and its downstream neural pathways promised to reveal the magic adipostat that could be pharmacologically tricked into generating weaker appetite and stronger thermogenic signals to bring excess body weight down. However, leptin does not seem to be able to cure or prevent common obesity in the larger population, although it might still be useful in a subpopulation of obese patients (10, 14, 20). Clearly, absence of leptin signaling has very powerful physiological effects, tricking a severely obese body into “thinking” it is too lean, eating all it can, and curbing energy expenditure (8). The hope is now to find the mechanism for leptin resistance and develop drugs that bypass resistance by targeting downstream neural processing steps such as the melanocortins.

Food intake is mainly controlled through the size and number of meals, and because humans typically eat only three meals, control of meal size is of crucial importance. Among the factors that determine meal size, taste and mechanosensory input from the oral cavity together with satiety signals generated by ingested food as it moves through and is absorbed by the gastrointestinal tract are considered direct controls (22). Motivational, cognitive, emotional, and external factors are considered indirect controls. The brain stem appears to be sufficient to implement the direct controls, while the hypothalamus and other forebrain areas are required for expression of the indirect controls, as illustrated by the fact that decerebrate rats stop ingesting orally infused glucose solutions just like intact rats but are unable to increase meal size after food deprivation (12). Since experiments in rodents with pharmacological doses revealed that leptin decreases food intake by decreasing meal size, but not meal frequency (9), leptin action on the adipostat circuitry of the hypothalamus with its descending projections to the caudal brain stem was thought to represent the mechanism by which long-term changes in adiposity modulate the direct controls of food intake.

However, leptin may also act directly at the level of the brain stem to modulate the process of satiation. The hybridization signal for the long form leptin receptor (Ob-Rb mRNA) was also found in the dorsal vagal complex, hypoglossal, trigeminal, lateral reticular, and parabrachial nuclei. Peripherally administered leptin increased both janus kinase signal transducer and activator of transcription (STAT3) phosphorylation, and suppressor of cytokine signaling 3 (SOCS3) mRNA not only in the hypothalamus but also in the NTS (15). In addition, leptin significantly suppressed food intake for 24 h when injected directly into the dorsal vagal complex, in a dose subthreshold when injected into the fourth ventricle (13). Furthermore, leptin receptors are also found in taste buds (16, 21), and leptin administration to normal mice suppresses responses of primary afferent gustatory fibers in the chorda tympani and glossopharyngeal nerve to sucrose and saccharin but not to other taste qualities (16). Since leptin receptor mRNA was demonstrated in mouse circumvallate taste buds, and no suppression of nerve activity was found in db/db mice lacking leptin receptors, the implication is that leptin acts directly on taste receptor cells to modulate sweet taste sensation.

For all the above discussed mechanisms, it is assumed that the source of the ligand is circulating leptin derived from adipose tissue. In this issue of the American Journal of Physiology, Peters and colleagues (19a) present evidence for a fundamentally different leptin action on food intake, satiation induced by stomach-derived leptin mediated by abdominal vagal afferents. It had been known that leptin is produced in the mucosa of the stomach and rapidly mobilized by feeding and high doses of exogenous CCK (1), but it was not clear what function this might serve. Peters and colleagues (19a) hypothesized that leptin released from gastric mucosal cells might act in a paracrine fashion on vagal afferents to generate a satiety signal. They tested the hypothesis by infusing leptin directly into the celiac artery in nonanesthetized rats trained to drink sucrose solution. Small doses of leptin infused into the celiac artery significantly decreased 15-min sucrose intake, and this effect was not observed in rats with subdiaphragmatic vagotomy or perivagal capsaicin—treatments aimed to selectively ablate vagal afferent fibers. It is unlikely that celiac artery leptin produced its effect by spilling into the systemic circulation because infusion of the same dose of leptin into the jugular vein did not reduce sucrose intake, and because the increases in circulating leptin were similar for both routes of infusion. Thus the results support the hypothesis that leptin of gastric origin acts on vagal afferents to suppress food intake. Additional support for such a mechanism comes from the observations that the long form of the leptin receptor (Ob-Rb) is expressed by a subset of nodose ganglion neurons (7) and that leptin modulates electrical activity of vagal afferent fibers innervating the gastrointestinal tract (24).

The fundamental difference, then, is the source of leptin and governance of its release by different factors. Leptin derived from adipose tissue is largely encoding adipose tissue mass and was thus referred to as adiposity signal. However, because of the rapid fall of plasma leptin levels induced by food deprivation and the rapid recovery by feeding, it appears to have also some signaling capacity as a short-term depletion/repletion signal, independent of fat stores. The factors determining release of leptin from the gastric mucosa remain to be fully understood.
characterized. Interestingly, while gastric leptin content is not significantly lower in 18-h food-deprived rats compared with ad libitum-fed rats, it was significantly reduced within 15 min of refeeding or when large doses of exogenous CCK were administered to these starved rats (1). This is consistent with a pool of gastric leptin that is rapidly released by ingested food and by the subsequent secretion of CCK. Future experiments with local perfusion of CCK-receptor antagonists and diets that differ in their ability to stimulate endogenous CCK secretion should be able to shed more light on this new mechanism.

This newly found role for gastric leptin extends the already long list of satiety signals involved in the direct control of meal size. We have known for more than two decades now that CCK is released from the small intestinal mucosa by dietary fat and protein and acts via sensory fibers of the vagus nerve to signal satiety to the brain (11, 23). In addition, the thousands of vagal afferent fibers innervating the gastrointestinal tract with specialized terminals in the external smooth muscle layers, myenteric plexus, and mucosa sense a host of other putative satiety signals, including chemical, gastric distension, and phasic motility (6). Furthermore, other hormones released by ingested food and circulating fuels have also been shown to generate satiety through indirect mechanisms (4, 19).

Having this extraordinary array of multiple satiety mechanisms, why is it that obesity is rapidly increasing worldwide? One explanation is development of leptin resistance brought about by changes in nutrition and other environmental factors within the last 20 years or so. The exact nature of these factors, and at what signaling step resistance develops, is currently hotly debated. Defects in blood-brain barrier function and intracellular signaling mechanisms in leptin-sensitive hypothalamic neurons brought about by high-fat diets have been implicated (2, 3, 18). Because the mechanism suggested by Peters et al. (19a) does not depend on the blood-brain barrier and may not be affected by dietary fat, it might be functioning normally in the obese state.

Another explanation for the recent increase in the prevalence of obesity is that there was no evolutionary pressure for leptin to suppress food intake once it reaches plasma levels, reflecting adequate adipose tissue mass. Having weak satiety signaling was advantageous for survival in times of frequent famines. However, in a changed environment full of relevant external signals and availability of food, weak satiety signals are easily overpowered by appetitive drive. One of the key questions in the fight against obesity is whether satiety signals can be manipulated to be stronger or whether it might be more fruitful to reduce the appetitive drive that can so easily override satiety mechanisms.

REFERENCES