Published in final edited form as:

Physiol Behav. 2011 April 18; 103(1): 21–24. doi:10.1016/j.physbeh.2010.11.013.

Adiposity Signaling and Meal Size Control

Timothy H. Moran and Ellen E. Ladenheim

Department of Psychiatry and Behavioral Sciences Johns Hopkins University School of Medicine
Baltimore, Maryland, USA

Abstract

Signaling from energy stores provides feedback on overall nutrient availability to influence food intake. Beginning with seminal studies by Woods and colleagues identifying insulin as an adiposity signal, it has become clear that such factors affect food intake by modulating the efficacy of within meal feedback satiety signals. More recent work with leptin has revealed actions of the hormone in modulating the efficacy of multiple gut feedback signals, identified the dorsal hindbrain as a site of signal integration and suggested both local and descending hypothalamic to hindbrain actions in mediating these effects. The original work by Woods and colleagues provided the necessary experimental paradigms for these advances.

Keywords

insulin; leptin; cholecystokinin; satiety signaling

The controls of food intake are multiple and complex. Signals arise from diverse sites and sources and understanding how they are integrated to control feeding remains one of the major tasks before us. There has been a recent resurgence of interest in how various feeding related signals combine and whether such interactions are additive or synergistic.

In this article, we will review early work that provided the paradigms and rationales for studying interactions between adiposity and satiety signaling and present an overview of how leptin acts to inhibit meal size through interactions with within meal feedback signaling.

In a 1974 Psychological Review paper (1), Steve Woods and colleagues first proposed a role for insulin in overall energy balance. Although the original proposal involved the relative relationships between levels of insulin and growth hormone, specific actions for insulin were postulated. Importantly, Woods pointed out that insulin circulated in direct relationship to the level of adiposity and therefore could be the critical feedback signal postulated in Gordon Kennedy's lipostatic hypothesis (2). Insulin was proposed to provide a feedback signal to the brain on overall availability of energy stores. Subsequent work demonstrated that centrally administered insulin inhibited food intake providing further support for this idea (3).

© 2010 Elsevier Inc. All rights reserved

Timothy H. Moran, Ph.D. Department of Psychiatry and Behavioral Sciences Johns Hopkins University School of Medicine Ross 618
720 Rutland Ave. Baltimore, MD 21205 410-955-2344 410-502-3769 (FAX tmoran@jhmi.edu).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Work in primates provided the first indication of central insulin's mode of action in feeding control. In 1986, Figlewicz and colleagues demonstrated that chronic intracisternal insulin altered sensitivity to intravenous administration of the intestinal satiety peptide cholecystokinin (CCK) in baboons (4). A dose of insulin that by itself had no effect on food intake, significantly enhanced the ability of CCK to reduce meal size. The manuscript concluded with the statement:

“In summary, our data support the concept that insulin may modulate food intake by influencing the ability of circulating gut peptides to suppress meal size.”

This was the first suggestion that a signal related to body energy stores would exert its effects on food intake by modulating within meal feedback satiety signaling. Subsequent work from the Woods laboratory in rats demonstrated that acute intraventricular injections of insulin at levels that were subthreshold for inhibiting food intake when given alone, enhanced the ability peripherally administered CCK to reduce meal size (5). These data were interpreted to imply that at lower body weights and thus lower levels of circulating insulin, a given release of CCK would be less satiating resulting in larger meal. With increasing body weight and increased circulating levels of insulin, the same release of CCK would be more satiating resulting in the intake of smaller meals. Thus, insulin could provide a critical signal for maintaining overall energy balance and contributing to the regulation of a body weight set-point.

With the discovery of leptin in 1994, the focus on adiposity signaling shifted from insulin to leptin (6). Leptin is the protein product of the *ob* gene. Its absence, as in the *ob/ob* mouse, results in hyperphagia and obesity. Leptin is synthesized in adipose tissue and circulates in direct proportion to the adipose mass (7). Leptin receptors are found in a variety of brain areas but are enriched in hypothalamic nuclei with documented roles in feeding control (8). Leptin is transported across the blood barrier (9) and either peripheral or centrally administered leptin inhibits food intake (10). Thus, leptin provides feedback signaling to the brain about the availability of stored energy and serves as a signal to modulate food intake in response to alterations in overall energy availability.

A number of laboratories examined the mode of action of leptin in inhibiting food intake. Leptin's actions on feeding were shown to be specific to the inhibition of the size of meals with no change in meal number (11–13). Thus, consistent with the demonstrations on the actions of insulin in modulating satiety signaling from the Woods laboratory, leptin also appeared to work through effects on the controls of meal size rather than affecting the factors that contribute to meal initiation.

This idea was directly tested using a similar paradigm to that of Riedy et al. (5) and in contrast to the work with insulin, there has been significant progress on the site and mechanisms through which such interactions could occur. As shown in Figure 1a, intraventricular administration of a dose of leptin that was subthreshold for affecting food intake when administered alone, enhanced the inhibition of food intake produced by a peripherally administered dose of CCK (14). The effects of the various treatments alone or in combination on neural activation in the nucleus of the solitary tract (NTS), the site of vagal afferent terminations within the NTS, revealed that the combination of leptin and CCK resulted in synergistic increases in neural activation as reflected by the presence of the immediate early gene *c-fos* (Figure 1b) (15). Similar data were generated by a number of laboratories (16–18).

The ability of leptin to magnify the degree of feeding suppression and NTS neural activation produced by within meal satiety feedback signaling is not specific to CCK. Leptin can also modulate the feeding suppression produced by other within meal feedback signals. Similar

to the leptin/CCK interactions, leptin has also been demonstrated to amplify the feeding inhibitory actions of gastric loads (15) and of the peptide bombesin (19). Potential interactions between the lower gut peptide glucagon like peptide 1 (GLP-1) and leptin have also been examined (20). Fasting attenuates the satiety action of GLP-1 and physiological leptin replacement during fasting reverses this effect. Surprisingly, while a GLP-1 agonist elicits c-fos in the NTS, leptin blocked rather than potentiated the c-fos responses suggesting a different mode of interaction of leptin that those that have been demonstrated for CCK and gastric distention.

As well as increasing the number of cells expressing c-fos, electrophysiological studies have demonstrated that leptin can increase the gastric distention induced firing rate of single NTS neurons (21). As shown in Figure 2, leptin administered into the ventricular system of the forebrain enhances the electrophysiological response to single NTS neurons to intragastric balloon distention. Thus, the mode of action underlying the leptin induced enhanced c-fos response to the various within meal feedback signals appears to represent an enhancement of the responsiveness of NTS neurons to ascending satiety feedback.

Although these studies identify the NTS as a site of integration for the actions of leptin to enhance satiety signaling, they did not directly address the site of action for leptin in inducing these actions. While leptin was administered into forebrain ventricles in the majority of these studies, leptin receptors are widely distributed in the brain (22) and the natural flow of CSF within the ventricular system would provide access to both potential forebrain and hindbrain sites for this action.

Work by Morton and colleagues examined a potential role for leptin receptors within the medial basal hypothalamus (23). They began by demonstrating that the Koletsky rat that has a genetic deletion of leptin receptors (and develops hyperphagia and obesity), had a reduced satiety response to peripheral CCK. Using viral gene transfer techniques, they specifically replaced leptin receptors in the medial basal hypothalamus with a focus on the arcuate nucleus, a site that has been implicated in the feeding inhibitory actions of leptin. Restoration of arcuate leptin signaling both reduced the size of spontaneous meals in the Koletsky rat and made them more responsive to exogenous CCK. These rats with restored arcuate leptin signaling also had enhanced NTS c-fos responses to CCK administration. These data supported the idea that the site of action for leptin in the controls of meal size was hypothalamic and depended upon a descending pathway from the hypothalamus to the NTS.

Also consistent with this view are data demonstrating that modulation of the targets of arcuate leptin signaling, NPY and melanocortins also resulted in alterations in the ability of within meal feedback signals to affect food intake and invoke NTS activation. Thus, NPY administration reduces the ability of CCK to inhibit food intake and induce NTS c-fos (24). NPY also reduces the gastric distention-induced activation of single NTS neurons (21). Results with modulation of melanocortin signaling have been less consistent. The forebrain administration of the melanocortin agonist MT-11 fails to affect CCK or duodenal nutrient induced satiety (24,25) but hindbrain administration of the melanocortin $\frac{3}{4}$ receptor antagonist diminishes the satiating effect of CCK and mice lacking melanocortin 4 receptor fail to respond to peripheral CCK administration (26).

Potential mediators of descending hypothalamic to NTS signaling mediating the actions of leptin in enhancing within meal satiety signaling have been investigated. Blevins and colleagues have demonstrated such a potential role for paraventricular nucleus (PVN) oxytocin expressing neurons. These neurons project to the regions of the NTS in which peripheral CCK results in c-fos activation (27) and hindbrain administration of an oxytocin

antagonist reduced the satiety actions of CCK and resulted in less CCK induced c-fos in the NTS (27). These data demonstrated that oxytocin neurons were appropriately positioned to mediate an action of leptin in meal size control and subsequent experiments directly assessed such a role. They demonstrated that leptin activated PVN oxytocin neurons and that administration of an oxytocin antagonist prevented the leptin induced enhancement of CCK satiety (28). Finally, a cytotoxin specifically directed at NTS neurons containing oxytocin receptors significantly attenuated the feeding inhibitory efficacy of CCK (29). Together, these data identified oxytocin containing PVN neurons in a descending hypothalamic/NTS pathway mediating hypothalamic leptin actions in affecting meal size.

A similar role has been suggested for PVN gastric releasing peptide (GRP) containing neurons. The PVN contains a population of GRP expressing neurons that project to the NTS (30). GRP mRNA expression in these neurons is sensitive to nutritional status, decreasing in response to fasting and increasing following melanocortin stimulation (31). Hindbrain administration of a GRP receptor antagonist increases food intake (32) and significantly attenuates the electrophysiological response of NTS neurons to PVN stimulation (33). Direct effects of a GRP antagonist on leptin-induced enhancement of CCK satiety are yet to be assessed.

Direct NTS leptin actions in enhancing within meal satiety signaling have also been proposed. NTS neurons express leptin receptors and hindbrain leptin administration does inhibit food intake (34). Importantly viral shRNA mediated downregulation of hindbrain leptin receptors attenuates CCK satiety (35). Given the rostral caudal direction of CSF flow, injections of leptin into forebrain ventricles could well have been acting through leptin induced stimulation of both forebrain and hindbrain sites, suggesting a distributed neural network with overlapping controls.

Summary

The idea that signals arising from the body's energy stores would affect food intake by modulating the efficacy of within meal satiety signaling was a novel one when originally proposed by Woods and colleagues in 1986 (4). Their work on the interaction between insulin and CCK in both nonhuman primates (4) and rats (5) provided the paradigm for assessing mechanisms of action for leptin in feeding control. Leptin has now been shown to modulate the efficacy of multiple within meal feedback signals, the NTS has been identified as a critical site of integration and both descending and direct hindbrain actions for leptin in mediating these effects have been demonstrated. While the original Woods proposal did not designate potential sites of action or underlying mechanisms for the modulation of satiety signaling by adiposity signaling, the conceptualization significantly advanced our overall understanding of these critical interactions.

Acknowledgments

This work was supported by NIH grant DK19302.

References

1. Woods SCDE, Vasselli JR. Metabolic hormones and the regulation of body weight. *Psychological Reviews*. 1974; 81:26–43.
2. Kennedy G. The role of depot fat in the hypothalamic control of food intake in the rat. *Proceedings of the Royal Society of London (Biol)*. 1953; 140:579–592.
3. Woods SC, Lotter EC, McKay LD, Porte D Jr. Chronic intracerebroventricular infusion of insulin reduces food intake and body weight of baboons. *Nature*. 1979; 282:503–505. [PubMed: 116135]

4. Figlewicz DP, Stein LJ, West D, Porte D Jr, Woods SC. Intracisternal insulin alters sensitivity to CCK-induced meal suppression in baboons. *Am J Physiol.* 1986; 250:R856–860. [PubMed: 3518496]
5. Riedy CA, Chavez M, Figlewicz DP, Woods SC. Central insulin enhances sensitivity to cholecystokinin. *Physiol Behav.* 1995; 58:755–760. [PubMed: 8559787]
6. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature.* 1994; 372:425–432. [PubMed: 7984236]
7. Havel PJ. Mechanisms regulating leptin production: implications for control of energy balance. *Am J Clin Nutr.* 1999; 70:305–306. [PubMed: 10479190]
8. Baskin DG, Seeley RJ, Kuijper JL, Lok S, Weigle DS, Erickson JC, Palmiter RD, Schwartz MW. Increased expression of mRNA for the long form of the leptin receptor in the hypothalamus is associated with leptin hypersensitivity and fasting. *Diabetes.* 1998; 47:538–543. [PubMed: 9568684]
9. Banks WA, Kastin AJ, Huang W, Jaspan JB, Maness LM. Leptin enters the brain by a saturable system independent of insulin. *Peptides.* 1996; 17:305–311. [PubMed: 8801538]
10. Campfield LA, Smith FJ, Guisez Y, Devos R, Burn P. Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. *Science.* 1995; 269:546–549. [PubMed: 7624778]
11. Flynn MC, Scott TR, Pritchard TC, Plata-Salaman CR. Mode of action of OB protein (leptin) on feeding. *Am J Physiol.* 1998; 275:R174–179. [PubMed: 9688976]
12. Eckel LA, Langhans W, Kahler A, Campfield LA, Smith FJ, Geary N. Chronic administration of OB protein decreases food intake by selectively reducing meal size in female rats. *Am J Physiol.* 1998; 275:R186–193. [PubMed: 9688978]
13. Kahler A, Geary N, Eckel LA, Campfield LA, Smith FJ, Langhans W. Chronic administration of OB protein decreases food intake by selectively reducing meal size in male rats. *Am J Physiol.* 1998; 275:R180–185. [PubMed: 9688977]
14. Emond M, Schwartz GJ, Ladenheim EE, Moran TH. Central leptin modulates behavioral and neural responsivity to CCK. *Am J Physiol.* 1999; 276:R1545–1549. [PubMed: 10233050]
15. Emond M, Ladenheim EE, Schwartz GJ, Moran TH. Leptin amplifies the feeding inhibition and neural activation arising from a gastric nutrient preload. *Physiol Behav.* 2001; 72:123–128. [PubMed: 11239989]
16. Barrachina MD, Martinez V, Wang L, Wei JY, Tache Y. Synergistic interaction between leptin and cholecystokinin to reduce short-term food intake in lean mice. *Proc Natl Acad Sci U S A.* 1997; 94:10455–10460. [PubMed: 9294232]
17. Wang L, Martinez V, Barrachina MD, Tache Y. Fos expression in the brain induced by peripheral injection of CCK or leptin plus CCK in fasted lean mice. *Brain Res.* 1998; 791:157–166. [PubMed: 9593872]
18. McMinn JE, Sindelar DK, Havel PJ, Schwartz MW. Leptin deficiency induced by fasting impairs the satiety response to cholecystokinin. *Endocrinology.* 2000; 141:4442–4448. [PubMed: 11108253]
19. Ladenheim EE, Emond M, Moran TH. Leptin enhances feeding suppression and neural activation produced by systemically administered bombesin. *Am J Physiol Regul Integr Comp Physiol.* 2005; 289:R473–R477. [PubMed: 15860644]
20. Williams DL, Baskin DG, Schwartz MW. Leptin regulation of the anorexic response to glucagon-like peptide-1 receptor stimulation. *Diabetes.* 2006; 55:3387–3393. [PubMed: 17130484]
21. Schwartz GJ, Moran TH. Leptin and neuropeptide y have opposing modulatory effects on nucleus of the solitary tract neurophysiological responses to gastric loads: implications for the control of food intake. *Endocrinology.* 2002; 143:3779–3784. [PubMed: 12239088]
22. Guan XM, Hess JF, Yu H, Hey PJ, van der Ploeg LH. Differential expression of mRNA for leptin receptor isoforms in the rat brain. *Mol Cell Endocrinol.* 1997; 133:1–7. [PubMed: 9359467]
23. Morton GJ, Blevins JE, Williams DL, Niswender KD, Gelling RW, Rhodes CJ, Baskin DG, Schwartz MW. Leptin action in the forebrain regulates the hindbrain response to satiety signals. *J Clin Invest.* 2005; 115:703–710. [PubMed: 15711637]

24. Moran TH, Aja S, Ladenheim EE. Leptin modulation of peripheral controls of meal size. *Physiol Behav.* 2006; 89:511–516. [PubMed: 16735044]
25. Azzara AV, Sokolnicki JP, Schwartz GJ. Central melanocortin receptor agonist reduces spontaneous and scheduled meal size but does not augment duodenal preload-induced feeding inhibition. *Physiol Behav.* 2002; 77:411–416. [PubMed: 12419417]
26. Fan W, Ellacott KL, Halatchev IG, Takahashi K, Yu P, Cone RD. Cholecystokinin-mediated suppression of feeding involves the brainstem melanocortin system. *Nat Neurosci.* 2004; 7:335–336. [PubMed: 15034587]
27. Blevins JE, Eakin TJ, Murphy JA, Schwartz MW, Baskin DG. Oxytocin innervation of caudal brainstem nuclei activated by cholecystokinin. *Brain Res.* 2003; 993:30–41. [PubMed: 14642828]
28. Blevins JE, Schwartz MW, Baskin DG. Evidence that paraventricular nucleus oxytocin neurons link hypothalamic leptin action to caudal brainstem nuclei controlling meal size. *Am J Physiol Regul Integr Comp Physiol.* 2004
29. Baskin DG, Kim F, Gelling RW, Russell BJ, Schwartz MW, Morton GJ, Simhan HN, Moralejo DH, Blevins JE. A new oxytocin-saporin cytotoxin for lesioning oxytocin-receptive neurons in the rat hindbrain. *Endocrinology.* 2010; 151:4207–4213. [PubMed: 20610562]
30. Lynn RB, Hyde TM, Cooperman RR, Miselis RR. Distribution of bombesin-like immunoreactivity in the nucleus of the solitary tract and dorsal motor nucleus of the rat and human: colocalization with tyrosine hydroxylase. *J Comp Neurol.* 1996; 369:552–570. [PubMed: 8761928]
31. Ladenheim EE, Behles RR, Bi S, Moran TH. Gastrin-releasing peptide messenger ribonucleic acid expression in the hypothalamic paraventricular nucleus is altered by melanocortin receptor stimulation and food deprivation. *Endocrinology.* 2009; 150:672–678. [PubMed: 18818295]
32. Ladenheim EE, Taylor JE, Coy DH, Moore KA, Moran TH. Hindbrain GRP receptor blockade antagonizes feeding suppression by peripherally administered GRP. *Am J Physiol.* 1996; 271:R180–184. [PubMed: 8760218]
33. Zhang X, Sun X, Renahan W, Fogel R. GRP mediates an inhibitory response of gut-related vagal motor neurons to PVN stimulation. *Peptides.* 2002; 23:1649–1661. [PubMed: 12217426]
34. Grill HJ, Schwartz MW, Kaplan JM, Foxhall JS, Breininger J, Baskin DG. Evidence that the caudal brainstem is a target for the inhibitory effect of leptin on food intake. *Endocrinology.* 2002; 143:239–246. [PubMed: 11751615]
35. Hayes MR, Skibicka KP, Lechner TM, Guarnieri DJ, DiLeone RJ, Bence KK, Grill HJ. Endogenous leptin signaling in the caudal nucleus tractus solitarius and area postrema is required for energy balance regulation. *Cell Metab.* 2010; 11:77–83. [PubMed: 20074530]

Leptin enhances the actions of CCK

Figure 1.

Enhancement of the satiety actions of CCK by leptin. Panel A: Effects of CCK, Leptin and the CCK/Leptin combination of 30 min food intake. * indicates significant suppression from Sal/Sal baseline. ** indicates significant suppression from CCK alone. Panel B: Dorsal hindbrain c-fos responses to CCK, Leptin and CCK/Leptin combination. * indicates significant enhancement from CCK alone. Reprinted from Emond et al., 1999 (14).

Figure 2.

Leptin amplifies the electrophysiological responses of NTS neurons to gastric distention. A. Single NTS neuronal response to 4 ml gastric load before and following icv leptin administration. B. Dose response relationship to gastric load pre and post leptin administration. * indicates significant elevation following leptin treatment. Reprinted from Schwartz and Moran, 2002 (21).