Brain Pathways Controlling Food Intake and Body Weight

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Evidence has existed for more than 50 years in support of the hypothesis that body energy stored in the form of fat is homeostatically regulated. Implicit in this concept is the existence of a biological system that operates dynamically over time to match cumulative energy intake to energy expenditure. For example, to compensate for weight loss induced by energy restriction, animals must enter a period of positive energy balance (i.e., energy intake greater than energy expenditure) that is sustained for as long as it takes to correct the deficit in body fat stores. Having reached this point, the animal must return to a state of neutral energy balance if stable fat mass is to be maintained. The identification of neuronal circuits in the hypothalamus that, when activated, exert potent, unidirectional effects on energy balance provides a cornerstone of support for this model. The additional finding that these central effector pathways are regulated by humoral signals generated in proportion to body fat stores, including the hormones insulin and leptin, helps to round out the picture of how energy homeostasis is achieved. The goal of this overview is to highlight the evidence that specific subsets of hypothalamic neurons containing specific signaling molecules participate in this dynamic regulatory process, and to put these observations in the larger context of a biological system that controls body adiposity.

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Adiposity Signals: Insulin and Leptin

The concept that humoral signals generated in proportion to body energy stores provide negative feedback to brain areas that control food intake and energy expenditure was first proposed by Gordon Kennedy some 50 years ago. He reasoned that if the brain is to engage compensatory mechanisms that influence energy balance when the stability of body fat stores is threatened, it must receive afferent input in proportion to the current level of body fat. Several criteria to be met by an afferent humoral signal involved in energy homeostasis can be considered: The signal should circulate in plasma at levels proportional to body fat content and should enter the brain in proportion to its circulating level; administration of the putative signal into the circulation or directly into the brain should reduce food intake and promote weight loss, whereas a deficit of this signal should have the opposite effect; and a signal transduction system that mediates the effects of the signal should be identifiable in brain areas known to control food intake and body weight. To date, the hormones insulin and leptin are the only molecules known to meet each of these criteria.

A role for insulin in the central nervous system (CNS) control of energy homeostasis was first proposed by Woods and Porte (1). This hypothesis was based on evidence that insulin circulates in proportion to body fat in humans and most other mammals, that insulin receptors are concentrated in brain areas involved in the control of food intake (such as the hypothalamic arcuate nucleus), and that administration of insulin directly into the brain results in dose-dependent reductions of food intake and body weight without evidence of toxicity or systemic illness (reviewed in Ref. 2). Subsequent studies revealed that circulating insulin enters the CNS via a saturable transport mechanism that can be downregulated in response to environmental stimuli that predispose to weight gain (e.g., consumption of a high fat diet) (3).

A major discovery in 1994 followed from the hypothesis that mice with mutation at the *ob* locus (*ob/ob*) are deficient in a key adiposity signal (4) since they exhibit sustained hyperphagia, reduced energy expenditure, and severe obesity (5). Since *ob/ob* mice have high insulin levels, as expected for their degree of obesity, the missing adiposity signal was unlikely to be insulin. Cloning of the *ob* gene by Friedman and colleagues (4) provided powerful support for the existence of a previously unknown adiposity signal, which they termed "leptin." This hormone is a secreted product of the adipocyte, and its deficiency is responsible

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for the severe obesity phenotype of *ob/ob* mice. Subsequent studies, including the identification of the leptin receptor, established that leptin meets the criteria delineated above for a humoral adiposity negative feedback signal, and studies now have begun to explore the mechanism(s) whereby leptin regulates neuronal circuits involved in energy homeostasis.

Although leptin plays a quantitatively more important role than insulin, several observations suggest that insulin and leptin exert overlapping effects on hypothalamic neurons involved in energy homeostasis. Both hormones cause sustained, dose-dependent decreases of food intake and body weight following intracerebroventricular infusion, whereas deficiency of either hormone causes hyperphagia (2). A role for neuronal insulin signaling in the control of body adiposity was confirmed by the recent finding that neuron-specific deletion of insulin receptors leads to increased body fat deposition (6). Impaired reproductive function is an additional component of the phenotype of these mice, and although the mechanism underlying this effect is unknown, it is noteworthy that mice lacking either leptin or its receptor have similar defects affecting the reproductive axis. These observations raise the possibility of crosstalk between signaling events downstream of insulin receptors and leptin receptors in key hypothalamic neurons, and studies currently are underway to address this hypothesis.

Although humans with severe obesity due to mutation of leptin or its receptor are now well described, most forms of human obesity are characterized by normal or increased food intake despite increased circulating levels of insulin and leptin, and are without any known defect in the receptors for these two adiposity signals. Therefore, common forms of obesity in both humans and animal models are hypothesized to involve resistance to the actions of insulin and leptin downstream of their neuronal receptors, affecting the brain pathways that mediate their effects on energy balance. Thus, the identification of these neuronal pathways and the means by which they become resistant to input from adiposity signals is a high priority.

Central Effector Pathways That Control Energy Balance

Insight into the location of neuronal targets for the action of insulin and leptin can be gained from the CNS distribution of insulin and leptin receptors. One of the few brain areas that contains high levels of both receptors is the hypothalamic arcuate nucleus, and two key neuronal subsets involved in energy homeostasis are also situated in this brain area. Neuropeptide Y (NPY) is a powerful orexigen that also reduces energy expenditure and, with repeated central administration, can readily induce obesity in rodents. In the hypothalamus, NPY is synthesized primarily by neurons located in the ventromedial aspect of the arcuate nucleus, and these cells are activated in response to negative energy balance (e.g., caloric restriction or starvation). In view of NPY's potent orexigenic effects, this activation of NPY neurons is proposed to contribute to hyperphagia triggered by loss of body fat, although controversy exists surrounding the precise contribution of NPY in such conditions (7, 8).

Opposing the actions of NPY are the melanocortins, peptides cleaved from the proopiomelanocortin (POMC) precursor molecule (9) that are produced by neurons in more dorsolateral subregions of the arcuate nucleus. Pharmacological administration of melanocortins such as α-melanocyte-stimulating hormone, directly into cerebral ventricles causes acute decreases of food intake and promotes weight loss (10). Evidence that these POMC neurons are involved in energy homeostasis stems from observations that both chronic caloric restriction and acute energy deprivation reduce POMC gene expression in the arcuate nucleus (11, 12), and that pharmacological blockade of CNS melanocortin receptors causes hyperphagia and weight gain (10). Thus, NPY and melanocortins have opposing effects on energy balance, and NPY and POMC neurons are reciprocally regulated in response to negative energy balance. The effect of weight loss to both increase NPY and reduce melanocortin signaling in the hypothalamus is thus hypothesized to play a key role in adaptive behavioral and autonomic responses that promote the recovery of depleted fat stores.

Current evidence suggests that regulation of both NPY and POMC neurons in response to changes of body fat mass involves changing input from insulin and leptin. For example, the effect of fasting to increase NPY gene expression in the arcuate nucleus, but not in other brain areas, can be inhibited by administration of either insulin (13) or leptin (14) directly into the brain. Moreover, genetic leptin deficiency in *ob/ob* mice leads to marked upregulation of NPY gene expression in the arcuate nucleus and this effect is reversed by leptin administration (15, 16). The reverse holds true for POMC neurons in the arcuate nucleus. Leptin administration to fasted animals increases hypothalamic POMC gene expression, whereas genetic leptin deficiency lowers POMC mRNA levels in a manner that is reversed by leptin administration (11). These observations provide compelling support for a model in which a change in the level of adiposity negative feedback signals (reflecting a proportionate change of body fat content) is transduced into adaptive changes of food intake and energy expenditure via a highly coordinated set of regulatory responses occurring within arcuate nucleus NPY and POMC neurons (17). By reducing input from adiposity signals, a period of energy deficit activates NPY while inhibiting POMC neurons, responses that are proposed to trigger an increase of food intake until the deficit is corrected. Conversely, involuntary overfeeding in normal rats (e.g., via infusion of nutrients directly into the stomach) causes anorexia via a mechanism dependent on increased melanocortin receptor signaling (18).

A fascinating aspect of melanocortin signaling in en-

ergy homeostasis surfaced when it was recognized that an endogenous melanocortin receptor antagonist is also synthesized within hypothalamic neurons. Known as agouti-related peptide (AgRP) (19), this molecule induces sustained increases of food intake upon central infusion by blocking hypothalamic melanocortin receptors. Neuronal AgRP is synthesized primarily (if not exclusively) in arcuate nucleus NPY-containing neurons, and virtually all NPY neurons in this brain area coexpress AgRP (20). These NPY/AgRP neurons are therefore remarkably specialized, as they are capable of increasing food intake not only by increasing NPY signaling, but by decreasing melanocortin signaling as well. Like NPY, expression of AgRP is strongly induced both by a period of negative energy balance and by genetic leptin deficiency (19, 20). More recent studies suggest that NPY/AgRP neurons also exert direct effects to inhibit melanocortin expression in adjacent POMC neurons (21).

Implications for the Pathogenesis and Treatment of Obesity

One of the benefits of our rapidly expanding understanding of the biological control of energy homeostasis is that it provides a framework within which to assess the role of specific molecules in the pathogenesis of obesity. For example, maintenance of normal body weight is predicted to require that leptin, signaling via leptin receptors in the hypothalamus, is able to activate POMC neurons and to thereby increase signaling at hypothalamic melanocortin receptors. Consistent with this model, genetic obesity occurs not only in mice bearing mutations of leptin or its receptor, but in mice with mutations of POMC (22) or the melanocortin 4 receptor (Mc4r, the principal melanocortin receptor implicated in the effect of melanocortins on food intake and body weight) (23). These observations prompted efforts to screen these genetic loci in cohorts of obese humans in search of genetic causes of obesity.

This effort has borne fruit. Thus, whereas single gene mutations causing human obesity were unknown as recently as 5 years ago, examples have now been reported in individuals with mutations of genes encoding leptin, leptin receptor, POMC, and Mc4r as well as other loci (24). The use of animal models to identify key molecules in energy homeostasis has therefore yielded important new insights into the genetic basis of human obesity. Although most of these monogenic obesity syndromes are rare, Mc4r mutations have been identified in up to 4% of obese human populations (24). In more common forms of obesity, however, the heritable contribution is polygenic, and studies using linkage analysis have identified several additional candidate loci that may play a role (25).

The identification of signaling molecules that are critical for energy homeostasis and are implicated in the pathogenesis of obesity has generated optimism that new, more effective approaches to obesity treatment will follow. Indeed, pharmaceutical companies worldwide are actively screening and testing drugs with activity at melanocortin receptors, leptin receptors, and NPY receptors, to name but a few. To date, this effort has not expanded the armamentarium of drugs available for obesity treatment, but this will likely change over time. Given the remarkably high and still increasing prevalence of obesity in many areas of the world (26), the market for such compounds is unparalleled, as is the potential benefit to those who suffer its adverse health consequences.

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1. Woods SC, Lotter EC, McKay LD, Porte D Jr. Chronic intracerebroventricular infusion of insulin reduces food intake and body weight of baboons. Nature **282**:503–505, 1979.
2. Woods S, Seeley RJ, Porte D Jr., Schwartz MW. Signals that regulate food intake and energy homeostasis. Science **280**:1378–1383, 1998.
3. Kaiyala KJ, Prigeon RL, Kahn SE, Woods SC, Schwartz MW. Obesity induced by a high-fat diet is associated with reduced brain insulin transport in dogs. Diabetes **49**:1525–1533, 2000.
4. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature **372**:425–432, 1994.
5. Coleman DL. Effects of parabiosis of obese with diabetes and normal mice. Diabetologia **9**:294–298, 1973.
6. Bruning JC, Gautam D, Burks DJ, Schubert M, Orban PC, Klein R, Krone W, Muller-Wieland D, Kahn CR. Role of brain insulin receptor in control of body weight and reproduction. Science **289**:2122–2125, 2000.
7. Erickson JC, Clegg KE, Palmiter RD. Sensitivity to leptin and susceptibility to seizures of mice lacking neuropeptide Y. Nature **381**:415–418, 1996.
8. Bannon AW, Seda J, Carmouche M, Francis JM, Norman MH, Karbon B, McCaleb ML. Behavioral characterization of neuropeptide Y knockout mice. Brain Res **868**:79–87, 2000.
9. Cone RD, Lu D, Koppula S, Vage D, Klungland H, Boston B, Chen W, Orth DN, Pouton C, Kesterson RA. The melanocortin receptors: agonists, antagonists, and the hormonal control of pigmentation. Rec Prog Horm Res **5**:287–318, 1996.
10. Fan W, Boston BA, Kesterson RA, Hruby VJ, Cone RD. Role of melanocortinergic neurons in feeding and the agouti obesity syndrome. Nature **385**:165–168, 1997.
11. Schwartz MW, Seeley RJ, Woods SC, Weigle DS, Campfield LA, Burn P, Baskin DG. Leptin increases hypothalamic proopiomelanocortin (POMC) mRNA expression in the rostral arcuate nucleus. Diabetes **46**:2119–2123, 1997.
12. Cheung CC, Clifton DK, Steinier RA. Proopiomelanocortin neurons are direct targets for leptin in the hypothalamus. Endocrinology **138**:4489–4492, 1997.
13. Schwartz MW, Sipols AJ, Marks JL, Sanacora G, White JD, Scheurinck A, Kahn SE, Baskin DG, Woods SC, Figlewicz DP, Porte D Jr. Inhibition of hypothalamic neuropeptide Y gene expression by insulin. Endocrinology **130**:3608–1616, 1992.
14. Schwartz MW, Seeley RJ, Campfield LA, Burn P, Baskin DG. Identification of targets of leptin action in rat hypothalamus. J Clin Invest **98**:1108–1106, 1996.
15. Stephens TW, Bashinski M, Bristow PK, Bue-Vallesky JM, Burgetti SG, Craft L, Prater J, Hoffman J, Huang HM, Kriasticinas A, Mackeltar W, Rostack PR, Schoner B, Smith D, Tinarley FC, Zhang XY, Metman M. The role of neuropeptide Y in the antiobesity action of the obese gene product. Nature **377**:530–534, 1995.
16. Schwartz MW, Baskin DG, Bukowski TR, Kuijper JL, Foster D,

Lasser G, Prunkard DE, Porte D Jr, Woods SC, Seeley RJ, Weigle DS. Specificity of leptin action on elevated blood glucose levels and hypothalamic neuropeptide Y gene expression in *ob/ob* mice. Diabetes **45:**531–535, 1996.

17. Schwartz MW. Central nervous system control of food intake. Nature **404:**661–671, 2000.
18. Hagan MM, Rushing PA, Schwartz MW, Yagaloff KA, Burn P, Woods SC, Seeley RJ. Role of the CNS melanocortin system in the response to overfeeding. J Neurosci **196:**2362–2367, 1999.
19. Ollmann MM, Wilson BD, Yang Y, Kerns JA, Chen Y, Gantz I, Barsh GS. Antagonism of central melanocortin receptors *in vitro* and *in vivo* by agouti-related protein. Science **278:**135–138, 1997.
20. Hahn TM, Breininger JF, Baskin DG, Schwartz MW. Coexpression of AgRP and NPY in fasting-activated hypothalamic neurons. Nat Neurosci **1:**271–272, 1998.
21. Raposinho PD, Castillo E, d'Alleves V, Broqua P, Pralong FP, Aubert ML. Chronic blockade of the melanocortin 4 receptor subtype leads to obesity independently of neuropeptide Y action, with no adverse effects on the gonadotropic and somatotropic axes. Endocrinology **141:**4419–4427, 2000.
22. Yaswen L, Diehl N, Brennam MB, Hochgeschwender V. Obesity in the mouse model of proopiomelanocortin deficiency responds to peripheral melanocortin. Nat Med **5:**1066–1070, 1999.
23. Huszar D, Lynch CA, Fairchild-Huntress V, Dunmore JH, Fang Q, Berkemeier LR, Gu W, Kesterson RA, Boston BA, Cone RD, Smith FJ, Campfield LA, Burn P, Lee F. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. Cell **88:**131–141, 1997.
24. Barsh GS, Farooqi IS, O'Rahilly S. Genetics of body-weight regulation. Nature **404:**644–651, 2000.
25. Comuzie AG, Allison DB. The search for human obesity genes. Science **280:**1374–1377, 1998.
26. Kopelman PG. Obesity as a medical problem. Nature **404:**635–643, 2000.