INTRODUCTION

The hypothesis that body energy stored in the form of fat is homeostatically regulated continues to receive extensive experimental support. The premise underlying this concept is that cumulative energy intake is matched to energy expenditure over time via a biological system that promotes stability of body fat mass. The adaptive response to weight loss induced by energy restriction, for example, is predicted to involve energy intake that exceeds energy expenditure (e.g., entry into a state of positive energy balance) that is sustained until the deficit in body fat stores is corrected. Once the individual has returned to their regulated level of body adiposity, a state of neutral energy balance must be established and defended if stable fat mass is to be maintained. The identification of neuronal circuits in the hypothalamus that are activated by changes in body energy stores and which exert potent, unidirectional effects on energy balance provides a cornerstone of support for this model. The additional finding that humoral signals generated in proportion to body adiposity, including the hormones insulin and leptin, regulate these neuronal pathways sheds further light on the organization of this homeostatic system. The goal of this paper is to review the neuronal and endocrine mechanisms that participate in the dynamic regulation of body energy stored in the form of fat.

INSULIN AND LEPTIN

If the brain is to engage compensatory mechanisms that influence energy balance when the stability of body fat stores is threatened, it stands to reason that it might receive afferent input that reflects changes in the level of body fat. If the effect of energy restriction to deplete body fat stores results in a lowering of the level of such afferent signals, one might predict that afferent humoral signals involved in energy homeostasis should act centrally to promote a state of negative energy balance and weight loss. Candidate adiposity signals might be expected to meet several criteria. First, they should circulate at concentrations that are proportional to body fat content and should enter the brain in proportion to its circulating level. Second, 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. Third, a signal transduction system for the putative signal(s) should exist in brain areas known to control food intake and body weight. As reviewed below, the hormones insulin and leptin meet each of these criteria, and are the only molecules known to do so.

Woods and Porte proposed a role for insulin in the CNS control of energy homeostasis some twenty-five years ago [1]. The foundation for this hypothesis included the observations that insulin levels circulate in proportion to body fat in humans and most other mammals, and that insulin receptors are concentrated in brain areas involved in the control of food intake (such as the hypothalamic arcuate nucleus). Moreover, administration of insulin directly into the brain yields dose-dependent decreases of food intake and body weight without evidence of toxicity or systemic illness [reviewed in [2]]. Subsequent studies revealed that circulating insulin enters the central nervous system via a saturable transport mechanism that can be downregulated in response to environmental stimuli that predispose to weight gain, including consumption of a high fat diet [3].

The hypothesis that mice with autosomal recessive mutation at the ob locus (ob/ob) are deficient in a key adiposity signal [4] was suggested by their sustained hyperphagia, reduced energy expenditure, and severe obesity phenotype [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. Clo-
ning of the ob gene by Freidman and colleagues in 1994 led to the discovery of a previously unknown adiposity signal, which they termed leptin [4]. This hormone is secreted by adipocytes, and its deficiency causes the severe obesity phenotype of ob/ob mice. The subsequent identification of the leptin receptor and demonstration that its expression in the CNS, like that of the insulin receptor, is concentrated in medial hypothalamic subnuclei including the arcuate nucleus, established that leptin meets the criteria delineated above for a humoral adiposity negative feedback signal.

While leptin appears to play a quantitatively more important role than insulin, several observations suggest that the two hormones 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 is characterized by increased food intake [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]. The phenotype of mice with neuron-specific deletion of insulin receptors is also characterized by hypothalamic impairment of reproductive function. While the mechanism underlying this disorder is unknown, it is noteworthy that the phenotype of mice lacking either leptin (ob/ob) or its receptor (db/db) have a similar defect in the hypothalamic control of 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 are actively investigating this hypothesis.

Common forms of obesity in both humans and animal models are characterized by elevated circulating levels of insulin and leptin, without any known defect in the receptors for these two adiposity signals. This fact suggests that resistance to the actions of insulin and leptin downstream of their neuronal receptors may play a key role in obesity pathogenesis. The identification of these neuronal pathways and the means by which they become resistant to input from adiposity signals is thus a high priority.

**NEURONAL PATHWAYS THAT CONTROL ENERGY BALANCE**

Clues to the identity of neuronal targets that mediate effects of insulin and leptin can be gained from the CNS distribution of insulin and leptin receptors. One of few brain areas that contains high levels of both receptors is the hypothalamic arcuate nucleus, and this brain area also contains two key neuronal subsets involved in energy homeostasis. Neuropeptide Y (NPY) is a powerful orexigen that also reduces energy expenditure. With repeated central administration, therefore, NPY promotes positive energy balance that readily induces obesity in rodents. Hypothalamic NPY-producing neurons are located in the ventromedial aspect of the arcuate nucleus, and are activated in response to negative energy balance (e.g., caloric restriction or starvation). Increased hypothalamic NPY signaling may therefore contribute to the genesis of hyperphagia triggered by loss of body fat, although controversy exists surrounding the precise contribution of NPY in this setting [7, 8].

Melanocortins are peptides cleaved from the proopiomelanocortin (POMC) precursor molecule [9] that are produced by neurons in more dorsolateral subregions of the arcuate nucleus and exert effects on energy balance opposite to those of NPY. A particularly well-studied melanocortin is alpha-melanocyte stimulating hormone (α-MSH), which decreases food intake and promotes weight loss following administration directly into cerebral ventricles [10]. Evidence that these POMC neurons are involved in energy homeostasis stems from observations that both chronic caloric restriction and acute energy deprivation reduce arcuate nucleus POMC gene expression [11, 12], and that pharmacological blockade or genetic deletion of CNS melanocortin receptors causes hyperphagia and weight gain [10]. Weight loss induced by energy restriction, therefore both increases NPY and reduces melanocortin signaling in the hypothalamus, and these responses are hypothesized to play a key role in adaptive behavioral and autonomic responses that promote the recovery of depleted fat stores.

An important mechanism whereby both NPY and POMC neurons are regulated in response to increases or decreases of body fat mass involves changing input from insulin and leptin. Evidence for this hypothesis includes the observations that the effect of fasting to increase NPY gene expression in the arcuate nucleus, but not in other brain areas, is inhibited by administration of either insulin [13] or leptin [14] directly into the brain. Moreover, genetic leptin deficiency in ob/ob mice strongly induces arcuate nucleus NPY gene expression, an effect that is reversed by leptin administration [15, 16]. Conversely, 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]. Based on these observations, we an others have hypothesized that a changing levels of adiposity negative feedback signals (reflecting a proportionate changes of body fat content) yield adaptive changes of food intake and energy expenditure via coordinate regulation of arcuate nucleus NPY and POMC neurons [17]. According
Improvements in our understanding of the biological control of energy homeostasis have generated a framework within which to investigate the role of specific molecules in the pathogenesis of obesity. One well-studied example is the hypothesis that normal energy homeostasis requires leptin to signal via leptin receptors in the hypothalamus, which in turn activates POMC neurons and increases signaling at hypothalamic melanocortin receptors. Support for this hypothesis, stems from the genetic obesity that occurs not only in mice bearing mutations of leptin or its receptor, but in mice with mutations of either 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] as well. Based on these observations, several groups launched efforts to screen these genetic loci in cohorts of obese humans in search of new causes of genetic obesity.

Whereas monogenic forms of human obesity were unknown until recently, this effort has identified families with severe obesity transmitted by autosomal recessive mutations of genes encoding leptin, leptin receptor, POMC, and Mc4r in addition to other loci [24]. These observations validate the use of animal models not only to identify key molecules in energy homeostasis, but to clarify the genetic basis of human obesity. While most of these monogenic obesity syndromes are rare, Mc4r mutations have been identified in up to 4 % of obese human populations [24, 25]. 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 [24, 25].

Based on evidence that pathways downstream of leptin and insulin are critical determinants of energy homeostasis, pharmaceutical companies worldwide are actively screening and testing drugs with activity at melanocortin receptors, leptin receptors, and NPY receptors, to name but a few. As the prevalence of obesity continues to increase in many areas of the world [26], the need for such compounds has never been greater. As knowledge of energy homeostasis continues to expand, optimism that this objective may be met in the not-too-distant future seems warranted.

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