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Leptin resistance and the response to positive energy balance

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Abstract

Animals readily reduce food intake and normalize body weight following a period of involuntary overfeeding, suggesting that regulatory systems are engaged to defend against excess weight gain. However, these data exist in the background of an ongoing obesity epidemic, where the ready availability of palatable, energy dense foods often leads to obesity. Currently we know very little about the mechanisms underlying the normalization of body weight following involuntary overfeeding, nor do we fully understand why select individuals successfully remain lean despite living in an obesigenic environment. Recent progress in the study of leptin signaling indicates that manipulations which enhance leptin sensitivity reduce food intake and attenuate diet-induced obesity, while reductions in leptin signaling predispose to obesity. While it remains unclear whether a failure or insufficiency in the weight regulatory system contributes to obesity, this work highlights the importance of this system for the regulation of body weight and its potential value for the treatment of obesity. Nonetheless, it is necessary to more clearly identify those mechanisms that protect lean individuals from weight gain and mediate the normalization of body weight that follows involuntary overfeeding, because it is only with this knowledge that we can clearly determine whether obesity is dependent on, or independent of, a failure in the weight regulatory system.

Keywords

Obesity; overfeeding; leptin resistance; hypothalamus

Introduction

Considerable progress has been made toward defining the physiological and cellular mechanisms regulating energy balance, particularly in response to weight loss. Acute and chronic periods of energy restriction induce significant changes in energy metabolism and behavior, and a reduction in circulating leptin appears to be a primary mediator of these changes. Preventing the fall of leptin is sufficient to attenuate many of the physiological events associated with negative energy balance, including alterations in energy expenditure, reproductive function, thyroid function, immune function, and neuroendocrine hormone secretion [1]. Low leptin levels also alter behavior and neural function, impinging on reward and memory, drug seeking behavior, electrical self-stimulation, conditioned-place preference, and the perception and response to food and food cues [2–4]. Thus settings of low leptin induce metabolic changes which preserve existing energy stores while simultaneously altering the brain such that the procurement and consumption of food becomes incredibly important. Leptin is certainly not the only component of this system, and the basic model continues to expand to

include additional hormones, neuropeptides, and brain regions contributing to the regulation of energy balance [5–9].

Despite our increasing understanding of this system, obesity remains a significant health concern [10]. When exposed to highly palatable, energy dense diets, many humans and animals readily gain weight and adiposity. However, there is significant variability in this response, with some individuals effectively resisting weight gain despite being exposed to an obesigenic environment [11,12]. Rodents also show a substantial individual variability in the susceptibility to diet-induced obesity [13–18]. While a variety of mechanisms could contribute to this variability, several lines of evidence suggest that genetic or developmentally programmed differences in the weight regulatory system could contribute to differences in individual predisposition to obesity [19–24].

Involuntary overfeeding

The wide variation in weight gain on a high-fat diet highlights the difficulties inherent in using this model to define the response to positive energy balance. Therefore, some have used models of involuntary overfeeding to study positive energy balance, and this work provides evidence of a robust adaptive response. When animals are overfed either via gavage or intragastric infusion, a marked reduction of voluntary food intake occurs in addition to changes in metabolism [25–27]. More importantly, this reduction in food intake persists well beyond the cessation of overfeeding, lasting days or weeks depending on the degree of overfeeding and the rapidity of weight loss. Thus the voluntary hypophagia is not simply due to the presence of excess nutrients in the gut, but is instead an adaptive mechanism resulting in voluntary weight loss after overfeeding. In addition, work combining overfeeding with parabiosis demonstrates that overfeeding one animal reduces adiposity and alters metabolism in the parabiotic partner [28,29]. These experimental paradigms provide strong evidence for an adaptive resistance to weight gain, at least when that gain is not being driven by voluntary consumption of highly palatable diets.

There is a distinct lack of information on the hormonal and molecular mechanisms mediating the adaptive response to involuntary overfeeding. A variety of hormones might contribute to this response, and evidence does indicate that overfeeding alters ghrelin, insulin and leptin levels [27,30–32]. However, the degree to which these hormones contribute to the persistent hypophagia and weight loss following the cessation of overfeeding is unclear. Available evidence does implicate hypothalamic melanocortin signaling in this process, as overfeeding increased POMC expression within the mediobasal hypothalamus and intracerebroventricular administration of the melanocortin receptor antagonist SHU9119 following overfeeding attenuated the spontaneous hypophagia [33]. This outcome supports the hypothesis that POMC neurons are activated by overfeeding and contribute to adaptive decreases in food intake in response to positive energy balance. The mechanisms by which POMC neurons detect positive energy balance remain unclear. In an earlier study by the same group, it was noted that CRH expression was also significantly increased by overfeeding, but levels of NPY were not significantly decreased [27]. Again, these observations were made at the peak of overfeeding and it is unclear if these changes persist beyond the overfeeding treatment. In summary, these data indicate that mechanisms are in place to resist weight gain, as overfed animals to not remain at elevated body weights but instead spontaneously return to normal levels. While this adaptive response is most readily demonstrated when overfeeding is involuntarily imposed, it can also be observed in select individuals in a free feeding environment. Unfortunately, we know relatively little about the biological underpinnings of this resistance to weight gain, making it difficult to determine why this system appears inadequate or non-existent in certain individuals.

Leptin resistance and obesity

Though the discovery of leptin energized the study of energy balance, much of the initial enthusiasm has waned with the realization that obesity is not a condition of leptin insufficiency but instead of leptin resistance. Though the existence of leptin resistance is well accepted, it remains ill-defined. Leptin resistance is often described as a state in which circulating levels are elevated coincident with ongoing hyperphagia and obesity. By this standard, most obese individuals are leptin resistant. Leptin resistance is also defined as a failure of exogenously administered leptin to suppress food intake. However, food intake is not the only physiological endpoint regulated by leptin, and it has been suggested that effects of leptin on endpoints such as cardiovascular function and sympathetic outflow may remain intact even when the regulation of feeding is lost [34]. Lastly, leptin resistance can also be defined from a molecular standpoint, as a failure of leptin to activate key signaling molecules within target neurons. Yet leptin activates multiple intracellular signaling molecules of which resistance is often only demonstrated for a few [35], and there is also evidence for variations in leptin activated Stat3 across the brain [36], such that leptin sensitivity may vary even within the same animal.

Molecular causes of leptin resistance

What is known about leptin resistance is that it involves at least two separate mechanisms, the first being reduced transport across the blood brain barrier and the second a reduced capacity for intracellular signaling within target neurons. A reduction in leptin transport across the blood brain barrier (BBB) has been demonstrated directly in obese animals [37], and additional work documents reduced sensitivity to peripheral leptin signaling prior to loss of central leptin sensitivity [38,39]. Yet it has not been demonstrated that alterations in leptin transport directly influence body weight or food intake in lean or obese animals, and thus the role of reduced transport in the etiology of obesity is not fully clear. For instance, would enhancing transport in obese individuals reduce body weight? These issues are complicated by the fact that the cellular mechanisms of leptin transport and its disruption in obesity are not fully resolved [40–42].

Obesity is also associated with reduced capacity for leptin signaling within target neurons [8]. This resistance is manifest by an attenuated response to direct brain leptin injections (which bypass the BBB), both in terms of food intake and activation of intracellular signaling. While leptin activates multiple intracellular signaling cascades, leptin resistance is almost exclusively characterized as a reduced activation of the transcription factor Stat3. Only recently has evidenced emerged demonstrating a reduced activation of PI3K signaling [35]. Thus whether specific signaling systems are variably affected remains an open question.

Progress has been made in identifying potential cellular mediators of biochemical leptin resistance, leading to the identification of two molecules; suppressor of cytokine signaling 3 (Socs3) and protein tyrosine phosphatase 1B (PTP1B). Socs3 is a member of a family of proteins produced in response to cytokine signaling which act as intracellular negative feedback signals [43]. Socs3 expression is induced by Stat3 signaling, and it in turns binds to the leptin receptor and blocks the activation of Stat3 [44]. Based on these observations, it was predicted that Socs3 might contribute to leptin resistance. Genetic approaches have confirmed this hypothesis, as mice bearing genetic modifications which delete Socs3 or inhibit its ability to bind the leptin receptor exhibit reduced food intake and body weight and lead to a resistance to diet induced obesity [45–47]. PTP1B is likewise implicated in leptin resistance. As a phosphatase, PTP1B binds to and dephosphorylates Janus Kinase 2 (Jak2), the initial tyrosine kinase mediating leptin receptor signaling [48,49]. Overexpression of PTP1B in vitro dampens signaling from the leptin receptor [50], and mice genetically deficient for PTP1B are lean and hypersensitive to leptin [48,49]. Deletion of PTP1B exclusively within neurons recapitulates the leptin hypersensitivity and resistance to diet-induced obesity [51], and pharmacological

inhibition of PTP1B enhances the effects of central leptin injection [52]. These data collectively indicate that PTP1B acts within the brain to tonically inhibit signaling from the leptin receptor.

The above observations support the hypothesis that Socs3 and PTP1B regulate leptin signaling, but questions remain as to whether these molecules are causal to leptin resistance. It is possible that PTP1B and/or Socs3 are constitutive regulators of leptin signaling, and that their deletion increases basal leptin signaling sufficiently to protect against resistance induced by other means. A central question therefore is whether changes in Socs3 and PTP1B directly induce leptin resistance, and whether this resistance is sufficient to produce obesity. Regarding Socs3, there is mixed evidence as to whether Socs3 is increased with obesity, with some studies failing to detect increases [53,54] but another detecting an increase specifically within the arcuate nucleus [36]. One interesting set of data concerns Socs3 in hibernators, which exhibit periods of hyperphagia and weight gain in anticipation of winter hibernation. Experimental manipulation of day length is sufficient to alter leptin sensitivity in these animals, and the induction of leptin resistance is associated with increased Socs3 expression [55,56]. One interpretation of this work is that increased Socs3 produces leptin resistance, allowing hyperphagia and weight gain. Other settings of physiologically appropriate weight gain, such as preganancy/lactation, are also associated with leptin resistance [57,58], leading to the hypothesis that leptin sensitivity may be biologically regulated as a means to control body weight.

Regarding PTP1B, there is relatively little information focusing specifically on changes in PTP1B with leptin resistance. Although some unpublished work indicates that PTP1B is unchanged with diet-induced obesity, our recent work using a model of aging induced leptin resistance suggests that PTP1B protein levels are increased locally within the mediobasal hypothalamus in association with leptin resistance, and that pharmacological inhibition of PTP1B improves leptin sensitivity in this setting [52]. We have more recently detected a significant increase in PTP1B in the mediobasal hypothalamus in response to diet-induced obesity (unpublished observations), reminiscent of the aforementioned increase of Socs3 selectively within the arcuate nucleus [36]. If increases in PTP1B or Socs3 indeed directly contribute to the induction of leptin resistance, then it is critical to identify the mechanisms underlying these changes and to demonstrate that experimental induction of either PTP1B or Socs3 is sufficient to reproduce leptin resistance and induce weight gain.

Leptin and the response to positive energy balance

While the above discussion focuses separately on the response to positive energy balance and leptin resistance, these issues converge in the topic of obesity. What evidence do we have that leptin contributes to a response to positive energy balance, and by extension that loss of this response might contribute to obesity? Studies of Socs3 and PTP1B not only illustrate the role of Socs3 and PTP1B in leptin signaling, they also demonstrate that enhancing leptin signaling reduces food intake and promotes a lean, obesity-resistant phenotype [45–49,52]. If leptin were only a starvation signal, then manipulations which enhance leptin sensitivity would have no effect on the upper limit of body weight. Instead, increasing leptin sensitivity reduces body weight and protects against diet-induced obesity. Alternative support comes from work in obesity prone and obesity resistant strains. As noted above, there is significant variation between and even within strains in the predisposition to obesity, indicating a significant genetic component to obesity risk. Obesity prone strains appear to have decreased insulin and leptin sensitivity even prior to the development of obesity [59,60], suggesting that reduced leptin sensitivity may predispose those strains to obesity. Support also comes from observations in hibernation and pregnancy [55–58]. In these settings, hyperphagia and weight are physiologically necessary, and it appears that leptin resistance is biologically programmed in order to facilitate this weight gain. These observations suggest that leptin normally acts to limit

weight gain, because otherwise there would be no need to induce leptin resistance. Lastly, previously described studies combining overfeeding and parabiosis indicate that the parabiotic partner of an overfed animal reduces body adiposity in response to a “perceived” state of positive energy balance [28,29], with circulating signals underlying this response.

Taken together, these observations indicate that leptin is not simply a signal of negative energy balance, but that increases in leptin act to limit weight gain and adiposity. Loss of leptin sensitivity predisposes to obesity just as increases in leptin sensitivity protect against it. Currently it is unclear whether leptin resistance represents a pathological syndrome or if instead leptin sensitivity is biologically regulated to facilitate weight gain. The existence of molecules which down-regulate leptin sensitivity suggests an underlying biological mechanism, but it remains possible that these and other molecules become disrupted in our modern environment. As such, additional work is needed to define those events that are casual to the initial development of leptin resistance and then test whether they are sufficient to reproduce obesity. Even more so, it is apparent that we know very little about those mechanisms that mediate the normalization of body weight following forced overfeeding and which protect lean individuals from obesity. Because these settings represent appropriate regulation of body weight, they provide an opportunity to define the key components of the adaptive response to positive energy balance and then use this knowledge to determine if obesity is due to a failure in this regulatory response.

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