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Appetite control and energy balance regulation in the modern world: Reward-driven brain overrides repletion signals

Huiyuan Zheng, **Natalie Lenard**, **Andrew Shin**, and **Hans-Rudolf Berthoud**
Neurobiology of Nutrition Laboratory, Pennington Biomedical Research Center Louisiana State University System, Baton Rouge, Louisiana, USA

Abstract

Powerful biological mechanisms evolved to defend adequate nutrient supply and optimal levels of body weight/adiposity. Low levels of leptin indicating food deprivation and depleted fat stores have been identified as the strongest signals to induce adaptive biological actions such as increased energy intake and reduced energy expenditure. In concert with other signals from the gut and metabolically active tissues, low leptin levels trigger powerful activation of multiple peripheral and brain systems to restore energy balance. It is not just neurons in the arcuate nucleus, but many other brain systems involved in finding potential food sources, smelling and tasting food, and learning to maximize rewarding effects of foods, that are affected by low leptin. Food restriction and fat depletion thus lead to a "hungry" brain, preoccupied with food. In contrast, because of less (adaptive thrifty fuel efficiency) or lost (lack of predators) evolutionary pressure, upper limits of body weight/adiposity are not as strongly defended by high levels of leptin and other signals. The modern environment is characterized by increased availability of large amounts of energy dense foods and increased presence of powerful food cues, together with minimal physical procurement costs and a sedentary lifestyle. Much of these environmental influences impact cortico-limbic brain areas concerned with learning and memory, reward, mood, and emotion. Common obesity results when individual predisposition to deal with a restrictive environment as engraved by genetics, epigenetics, and/or early life experience, is confronted with an environment of plenty. Therefore, increased adiposity in prone individuals should be seen as a normal physiological response to a changed environment, not in pathology of the regulatory system. The first line of defense should ideally lie in modifications to the environment and lifestyle. However, because such modifications will be slow and incomplete, it is equally important to gain better insight how the brain deals with environmental stimuli and to develop behavioral strategies to better cope with them. Clearly, alternative therapeutic strategies such as drugs and bariatric surgery should also be considered to prevent or treat this debilitating disease. It will be crucial to understand the functional crosstalk between neural systems responding to metabolic and environmental stimuli, i.e. crosstalk between hypothalamic and cortico-limbic circuitry.

Keywords

Neural control of appetite; metabolic need; internal depletion signals; environmental food cues; cortico-limbic systems; food reward; leptin; obesity

Corresponding author: Hans-Rudolf Berthoud Pennington Biomedical Research Center Neurobiology of Nutrition Laboratory 6400 Perkins Road Baton Rouge, LA 70808 Ph: 225-763-2688 Fax: 225-763-0260 berthohr@pbrc.edu.

Introduction

The obesity epidemic continues unabated with no cure in sight. By increasingly affecting children and adolescents it is threatening to roll back much of the significant progress made in developed countries during the last century in living healthy and independent lives and in creating social harmony and economic productivity. The discovery of leptin over a decade ago spawned great hope for an end to the obesity crisis, like the discovery of insulin essentially cured type 1 diabetes half a century ago. That this has not happened, at least not yet, has been the subject of great debate. How is it possible that the ostensibly perfect negative feedback signal regulating adiposity permits accumulation of excessive body fat in the first place and why does leptin treatment not reverse obesity?

In this brief review, we will argue that the inherent asymmetry in the adaptive response to famine and feast may be responsible for the fact that simply changing the food environment can push adiposity of a population upwards and result in increased prevalence of obesity. We will review the emerging literature showing that low leptin together with other hormones and metabolites signaling relative decreases in nutrient supply powerfully invoke neural mechanisms of reward, motivation, and decision-making, and how this is exploited by the modern environment and lifestyle. We will argue that homeostatic defense of the upper limits of adiposity are inherently weakened by genetic predisposition and/or rapid and reversible development of resistance to metabolic feedback signals such as leptin. Finally, we will outline the distributed neural systems involved in appetite control and energy balance regulation and highlight the importance of crosstalk between the systems traditionally linked to metabolic regulation and processing of cognition, reward, and emotions.

Strong defense of adequate nutrition and the lower limits of adiposity

Procurement and availability of sufficient energy and essential nutrients is defended by a complex system consisting of fail-save, redundant pathways (1,2). Larger animals, including humans, can endure considerable periods without food by burning fat stored in significant depots and reducing energy expenditure. Smaller animals often do not have significant fat stores and fall into torpor for survival. In either case, hunger is strongly expressed at least initially. To organize these life-saving responses we rely on accurate sensors of the internal milieu and the external world, flexible and adaptive integrators that make sense out of all this diverse input, and powerful effectors that act both on the input and output arms of energy balance. The coordinator of this concerted effort to prevent nutrient depletion and restore energy supply is the brain. Food restriction and fat depletion lead to a “hungry” brain, preoccupied with food.

Research efforts in the post-leptin discovery era have mainly focused on the “metabolic brain”, identifying some of the crucial neural circuits in hypothalamus and hindbrain. Clearly, the hypothalamic neurocircuitry is crucial for body energy homeostasis as indicated by the development of obesity or leanness after loss or gain of function manipulations of its main components [e.g. (3)]. It is now thought that the mediobasal hypothalamus is the main hub for sensing availability of nutrients and for generating an integrated adaptive response to deviations from adiposity levels that are appropriate for a set of given internal and external conditions (4,5). Although this circuit is assumed by many to regulate body weight and adiposity within a narrow set point, much like a thermostat controls room temperature, this view has been largely abandoned in favor of a more flexible regulator that can learn from past experience and adapt to changing environmental factors (floating set point). Arguably, the major force “designing” the system was the constant struggle throughout evolution to find enough food for survival, resulting in a very strong defense of the lower limits of adiposity.

However, to understand how metabolic need is translated into strong behavioral actions that successfully compete with other motivated behavior, the role of the "cognitive and emotional brain" can no longer be neglected.

Cortico-limbic pathways coordinate metabolic need with the external world

It is clear that the neurocircuitry originating from the primary energy sensors in the arcuate nucleus described above is embedded in a much larger neural system that allows adaptation and coordination of metabolic needs to the demands and intricacies of the prevailing environment. For example, it does not make sense for the hungry vole to leave the burrow if the weasel waits outside. In fact, much of the brain has evolved to take care of hunger ever since mobile life forms emerged. Although procuring food in our modern environment is no longer difficult or potentially hazardous, it used to be a demanding task for most of the last 5 million years. Even more primitive invertebrate animals such as honey bees and ants use elaborate navigation and communication strategies to secure food sources and guarantee survival for the individual as well as society (6-8).

We remember past experiences with foods, particularly if the experience was out of the ordinary. A growing number of studies suggest that representations of experience with foods are generated in the orbitofrontal cortex, an area in the prefrontal cortex that receives converging information through all sensory modalities (9). Therefore, representations contain a number of sensory attributes, including shape, color, taste, and flavor, as well as links to time, location, social context, cost, and reward expectation (9,10). The orbitofrontal cortex is in intimate contact with other cortical areas, particularly the anterior cingulate, perirhinal and entorhinal cortices, as well as with the hippocampal formation and the amygdala, often collectively referred to as paralimbic cortex [for review see (9)]. It is within these areas that polymodal representations are thought to be available as working memory for constant updating.

A strong basic drive or motivation was necessary to leave the safety of a burrow or cave and procure nutrients in a dangerous environment with predators and toxic plants. Emotions evolved as a mechanism to reinforce beneficial and suppress potentially harmful stimuli and behaviors. For example, the sweet taste of certain foods and the process of satiation are associated with positive emotions that augment the motivational drive to find food and eat. Similar to sexual pleasure, the feelings of satisfaction and well being generated by eating result in strong motivation to engage in these behaviors again. The reward value of a particular food is bundled with the other attributes into the stored representations discussed above. Thus, life is all about learning how specific behavioral responses or actions lead to positive emotions or reward in the future.

An expanded view of energy homeostasis

It was originally thought that the classic nutritional feedback signals such as leptin, insulin, gut hormones, and circulating nutrients themselves, act mainly on a few areas of the brain such as specific parts of the hypothalamus and brainstem. However, recent studies suggest that these metabolic signals have a much broader influence on brain functions.

For example, leptin has been shown to modulate food-related sensory input signals of all modalities even at early stages of processing, so that low leptin levels can dramatically lower detection thresholds of external stimuli signaling availability of nutrients (11-14). Leptin and insulin can also act directly on mesolimbic dopamine neurons to modulate 'wanting' of food (15-17). Neural activity in the nucleus accumbens elicited by visual food stimuli is very high in genetically leptin-deficient adolescents and promptly returns to normal levels upon leptin administration. While in the leptin deficient state, nucleus accumbens activation was positively

correlated with ratings of liking in both the fasted and fed state, it was correlated only in the fasted state after leptin treatment and in normal individuals (18). The lower gut hormone PYY (3-36), which has now been convincingly demonstrated to suppress food intake in humans and rodents(19), also modulates activity of the ventral tegmental area (VTA) and ventral striatum (20). In contrast to leptin, the gut hormone ghrelin appears to facilitate foraging behavior and increase reward processing as part of its orexigenic action (21-25).

Dieting in overweight or obese humans has a very high failure rate, with most of them developing strong food cravings and inevitable relapse. The mechanisms of this paradoxical behavior have not been clear. The homeostatic regulatory system could be expected to cooperate in voluntary weight loss not make it difficult. However, comparing brain activity changes elicited by visual food stimuli in obese subjects before and after losing 10% body weight through dieting revealed the anatomy of a "hungry" brain. It is important to note that after a 10% weight loss these individuals were still obese with lots of excess adipose tissue. Still, looking at pictures of food evoked much larger changes in brain activity after this moderate weight loss. Although activity changes were found in the traditional homeostatic areas of hypothalamus and brainstem, many cortico-limbic areas involved in cognitive and emotional functions were most strongly affected by the weight loss (26). Importantly, most of these changes were fully reversed after leptin administration, and leptin treatment during dieting increased the chance to reach the weight loss goal and prevent relapse in another cohort of obese patients (27).

Thus, the traditional view of neural circuits regulating energy homeostasis has been expanded to include neural mechanisms of learning and memory, reward, attention, decision-making, mood, and emotionality. Adequate supply of energy is simply too important as not to include these powerful neural processes. To distinguish eating driven by internal, metabolic hunger signals from eating driven by hedonic, environmental signals in the absence of metabolic need, the terms "homeostatic" and "non-homeostatic" controls of appetite have recently been adopted (28-31). In light of the intimate neural interactions between these two classes of signals, this distinction may have been premature. Metabolic signals can modulate the cortico-limbic systems involved in higher brain functions, and the cortico-limbic systems can hijack the behavioral/metabolic effector mechanisms controlling energy balance. Together they serve one purpose – to maintain an optimal internal millieu in harmony with the external world.

Why does feedback from nutrient repletion signals not prevent obesity?

Weak defense of the upper limits of body weight

Evolutionary pressure has also existed to defend the upper limits of adiposity and, perhaps more likely, body weight (32). Disadvantages of elevated body weight are evident in the relationship between prey and predator – a heavier rodent is more likely to become prey of a weasel or bird compared to a lean rodent. Humans too were prey of larger predators, but the selection pressure for leanness disappeared with the use of weapons, fire, and shelter. The loss of selection pressure allowed the upper boundaries of adiposity and body weight to drift upwards by random genetic mutations over the last 2 million years or so (32).

Natural resistance to negative feedback signals

We now know that in most humans, obesity is a state of leptin resistance with high circulating leptin levels, and the finding that very few obese patients respond favorably to exogenous leptin was a major disappointment (33,34). Animal studies have shown that the same thing happens to laboratory rats and mice, domesticated animals like cats and dogs, as well as wild animals like polar bears and baboons, when they are exposed to human-like diets high in fat, sugar, and energy (35,36). Therefore, in contradiction to all the body weight set point and adipostat

theories positing leptin as the key negative feedback signal, slowly increasing circulating leptin levels do not prevent development of obesity in many individuals. Rises in other anorexigenic hormones such as insulin and amylin, as well as metabolites such as glucose and fatty acids are also not doing their expected job, and neither do decreases in the orexigenic gut hormone ghrelin. If prone individuals are exposed to the modern environment, the energy balance system simply equilibrates at a new higher level of body weight/adiposity, completely disregarding absolute values of feedback signals. This suggests that there is no predetermined set point for body weight/adiposity regulation, but that body weight/adiposity is defended within a range that depends on environmental conditions and individual predisposition.

Dependence of body weight/adiposity on environmental conditions should not be too surprising, as it makes a lot of sense for an organism to store extra energy for a rainy day. This is illustrated in seasonal animals, where leptin is ineffective in curbing appetite during summer, when food is abundant (37). The modern human environment could thus be regarded as the equivalent of continuous “summer” with natural leptin resistance. Before the modern era, this “summer” used to be broken by winters and famines that quickly restored leptin sensitivity. This seems to be confirmed by better success with leptin-treatment when it is given as an adjunct to moderate food intake restriction (27,38). A state of natural leptin resistance may be accomplished by increased expression of negative modulators of leptin receptor signaling. These intracellular signaling molecules could act as rapid molecular switches to turn leptin sensitivity on and off, depending on a particular combination of internal and external factors.

The modern environment acts on cortico-limbic systems to over-stimulate food intake

The major direct environmental factors thought to contribute to increased energy intake are availability, portion size, energy density, palatability, variety, and presence of food cues. Other important factors indirectly leading to poor food choice and overeating can be found in agricultural policies, pricing strategies, socioeconomic status, level of education, and stress vulnerability. The potential obesogenic role of many of these factors and recommendations for dealing with them have been reviewed recently [e.g. (39,40)]and will not be further discussed here.

While there has been a flood of studies demonstrating the acute food intake stimulatory effects of such environmental factors [e.g. (41,42)], or correlations of exposure to such factors with body mass index (43), few controlled interventional studies have demonstrated cumulative effects on food intake and increases in body weight by selectively changing one of these factors. In one such controlled clinical study, it was shown that increased portion size leads to significantly increased energy intake and weight gain over a period of 11 days (44). Many more such studies will be necessary to determine the relative importance of each factor and the capacity to interact with other factors in specific populations. However, it is already quite clear that the modern food environment has changed, and promotes increased energy intake and sedentary behavior.

The modern environment primarily impinges on higher brain functions such as learning and memory, reward optimization, attention, planning, and execution, organized mainly in cortico-limbic circuits. As discussed above, these brain systems are essential for efficient food procurement and they are specifically targeted by the advertising industry (45-47). As shown by using subliminal stimuli, such processes of memory formation and recall, reward evaluation, and preparation for motivated actions often take place outside awareness and thus partially escape conscious executive control (48,49).

Conclusions

The relative ineffectiveness of current pharmacological and dietary approaches to prevent or reverse obesity makes sense when considering the complex and redundant neural systems conferring the strong basic drive to eat. The lower level of body weight/adiposity is staunchly defended. Low leptin and other signals resulting from inadequate nutrient reserves turn the brain rapidly into a “hungry machine”. The slightest relative drop in customary nutrient availability, even at elevated body weight levels, triggers a powerful response. On the other hand, the upper level of body weight is only poorly defended, particularly in genetically prone individuals. This asymmetric response pattern in which the “eat more” command is dominant over the “stop eating” command inevitably leads to slow and incremental weight gain. Not unlike the ratcheting action of a car jack, exposure to the environment of plenty pushes body weight only in one direction - upwards.

Realizing that in this scenario, the primary cause of obesity is seen in changes in environmental and lifestyle changes, prevention and treatment therapies should first focus on reversing or modifying some of the most salient changes. Secondly, understanding the neural mechanisms translating environmental stimuli into behavioral actions will be crucial for the development of behavioral modification and pharmacological intervention therapies. Finally, development of pharmacological or surgical tools bolstering existing internal feedback signals or enhancing their downstream signaling capacity should also be continued.

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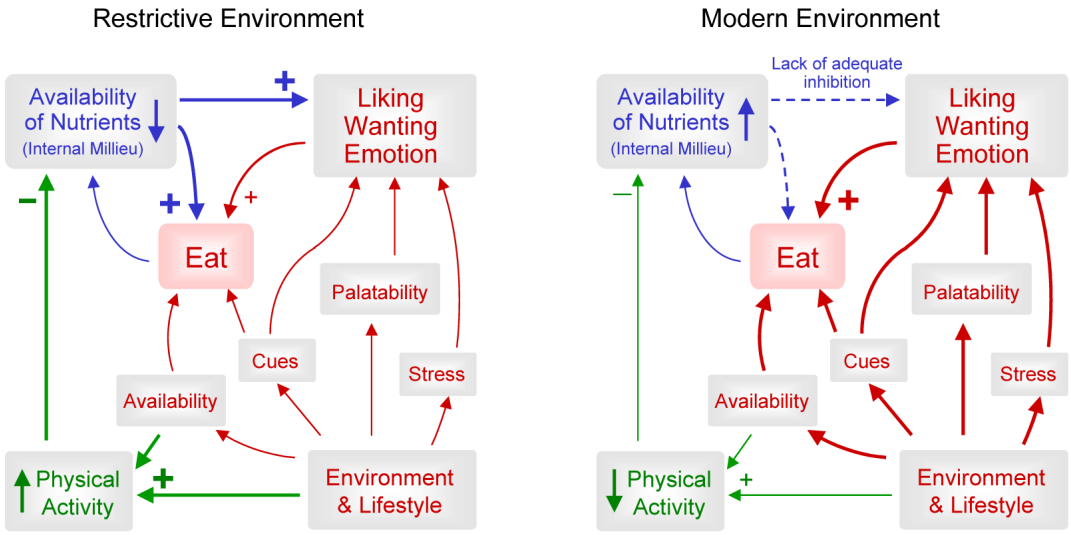

Fig. 1.

Schematic diagram showing major factors determining food intake and energy balance in restrictive and modern environments. The availability of nutrients (internal millieu) is detected by a plethora of distributed sensors and controls food intake directly through classical hypothalamic-brainstem pathways and indirectly through modulation of food reward processes in cortico-limbic structures (blue arrows). Low nutrient availability as, for example, signaled by low leptin levels, produces very strong sensitization of cognitive and hedonic mechanisms enabling procurement and ingestion of food as well as generating high reward and satisfaction. This system evolved in order to guarantee adequate nutrient supply in restrictive environments requiring a high physical activity level. The modern environment and lifestyle are characterized by high food availability, abundant food cues, and high food palatability (red arrows), all enhancing food intake either directly or through the same cortico-limbic systems easily sensitized by nutrient depletion signals. In addition, the built environment, sedentary lifestyle, and low procurement costs lead to decreased physical activity and in turn, increased nutrient availability (green arrows). Obesity develops in prone individuals that either efficiently translate exaggerated hedonic, cognitive, and/or emotional pressure exerted by the modern environment and lifestyle into increased eating, or individuals in which energy repletion signals are not able to suppress hedonic eating, or both.