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Eating for pleasure or calories

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Abstract

A changing environment and lifestyle on the background of evolutionary engraved or perinatally imprinted physiological response patterns is the foremost explanation for the current obesity epidemic. However, it is not clear what the mechanisms are by which the modern environment overrides the physiological controls of appetite and homeostatic body weight regulation. Major advances have been made regarding cross talk between metabolic signals and the cognitive/emotional brain that primarily deals with the environment. On one hand, metabolic signals such as leptin and ghrelin have previously unexpected direct effects on learning and memory, as well as liking and wanting. On the other hand, brain areas involved in reward, cognition, and executive control, can override metabolic regulation by talking to the hypothalamus.

Introduction

Obesity and the metabolic syndrome are rapidly increasing, with every third child born in the USA predicted to develop type 2 diabetes later in life. Although the primary cause of this epidemic is still disputed, the enormous pressures on energy balance provided by the modern environment and lifestyle remain the most plausible explanation. Here, we review recent literature dealing with the potential physiological mechanisms allowing these environmental and lifestyle pressures to override the normal controls of food intake and homeostatic regulation of energy balance. We first look at the multiple neural systems controlling appetite and energy balance, with particular emphasis on where and how metabolic signals modulate neural functions not normally associated with homeostatic regulation, such as cognition, reward, and emotion. We then examine evidence for the reverse modulation of metabolic processes and homeostatic regulation by cognitive, hedonic, and emotional processes. Lastly, the elusive critical mechanism responsible for increased food intake and development of obesity in prone individuals is discussed.

The multiple neural systems controlling food intake and energy balance

The major components of the distributed neural system controlling food intake and energy balance are shown in Fig. 1 and have been reviewed extensively before [1,2]. For the purpose of this discussion, it is important to note that the limited view of a few, mainly hypothalamic “centers”, that was propagated by the molecular engineers riding the tails of the discovery of leptin, was gradually replaced during the last 10 years by a much more complex and distributed system, notably including the caudal brainstem and various cortico-limbic systems. It is now increasingly recognized that cognitive, hedonic, and emotional neural processes play important

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roles in energy intake and expenditure and the resulting energy balance. To acknowledge this apparent dichotomy, the terms “homeostatic” and ”non-homeostatic” controls and systems have also been used. However, realizing that the two systems are intimately linked to serve overall homeostasis in a given environment, such a distinction is no longer useful.

Modulation of sensory, hedonic, and cognitive processing of food-related stimuli by metabolic signals

Sensory processing of food-related stimuli

After its discovery, leptin was originally thought to selectively modulate activity of POMC and NPY neurons in the arcuate nucleus of the hypothalamus. It has since been shown to act on many more neurons. Leptin also modulates the sensitivity of taste receptor cells in the oral cavity [3], vagal mechanoreceptors in the gut [4], olfactory detection in the olfactory bulb [5], and visual perception of food [6]. It thus appears that leptin can gate food-related sensory input signals even at early stages of processing. Interestingly, leptin (ob/ob) and leptin receptor (db/db) deficient mice find buried food about 10 times faster than wildtype mice, and this difference disappears after injection of leptin in ob/ob mice [7]. These findings suggest that low levels or absence of leptin-signaling dramatically heightens olfactory detection of food.

Mnemonic representations of experience with food

A growing number of electrophysiological recording studies in monkeys and neuroimaging studies in humans suggest that representations of experience with foods are generated in the orbitofrontal and insular cortex. These areas receive converging information through all sensory modalities [8] and representations contain any number of sensory attributes, including shape, color, taste, and flavor, as well as links to time, location, social context, and reward value. The orbitofrontal cortex is in intimate contact with other cortical areas, such as the prefrontal, anterior cingulate, insular, perirhinal, and entorhinal cortices, as well as with the hippocampal formation and the amygdala, collectively often referred to as paralimbic cortex. It is within these areas that polymodal representations of experiences with foods are thought to be stored, updated and retrieved for guiding future appetitive behavior. Some of these areas and processes seem to be modulated by nutritionally relevant circulating hormones and metabolites.

The gut hormone ghrelin has been shown to directly act on hippocampal neurons and induce formation of new synapses in the CA1 region [9]. The ghrelin-induced changes in synaptic density were correlated with enhanced spatial learning. Ghrelin-deficient mice exhibited impaired spatial learning that was corrected by ghrelin administration [9]. These findings are consistent with the idea that ghrelin is involved in the appetitive phase of ingestive behavior when it is important to find food in the environment. It is plausible that the ghrelin-induced changes in hippocampal function facilitate the recall of stored representations of prior experience with food. This is indicated by human subjects reporting a vivid, plastic image of their preferred meal upon intravenous ghrelin infusion [10].

Obestatin derived from the same polypeptide precursor as ghrelin, but which rather suppresses food intake [11], also appears to enhance learning and memory and, in addition, produces an anxiolytic effect as indicated by increased percentage of open arm entries in the elevated plus maze [12]. There is also a considerable literature showing that leptin can modulate excitability of hippocampal neurons (as reviewed by [13]. Its dose-dependent differential effects on long-term potentiation and depression suggest that leptin can either facilitate or suppress memory functions [14,15]. While enhancement of spatial memory by orexigenic peptides such as ghrelin makes a lot of sense, it is not clear what the biological meaning is of enhanced memory function by anorexigenic peptides such as leptin and obestatin. One possible explanation is

that the anorexic peptides leptin and obestatin selectively enhance memory functions related to the experience of satiation. Amnesic patients with lesions including the hippocampus readily eat a second meal offered immediately after a full meal [16,17]. On the other hand, enhancing memory for a recent meal, by cuing study participants to recall items eaten at lunch, suppresses intake in an afternoon snack[16]. Studies in rats also suggest that the hippocampus may be critically involved with a specific type of memory inhibition function that could normally lead to the suppression of food intake[18].

The cortico-limbic brain structures involved in knowledge about food are not only modulated by hormones such as leptin involved in the longer-term regulation, but also by short-term fluctuations in available fuels. For example, activity of food-related neurons in the primate orbitofrontal cortex and amygdala depends on the level of metabolic hunger in a sensory-specific fashion [19]. Such neurons can associate the metabolic consequence of ingesting glucose with a specific taste, a behavior termed sensory-specific satiety. Similar findings were reported in humans by monitoring changes in blood flow associated with the acquisition of picture-odor contingencies before and after selective devaluation (satiation) [20]. These findings may thus provide a neurological explanation for the suggestion that in a contrast situation, the predictive reward value of a food-related odor that is not metabolically satiated becomes more salient, just as a sweet dessert becomes more desirable at the end of a savory meal.

Mechanisms of food reward

Reward from palatable food is processed by a complex neural system that includes the nucleus accumbens and ventral pallidum in the ventral striatum, the ventral tegmental area located in the midbrain and projecting through the mesolimbic dopamine system back to the nucleus accumbens, the prefrontal cortex, the hippocampus and amygdala. Nutritionally relevant hormones can modulate activity of the mesolimbic dopamine system. Leptin and insulin can act directly on mesolimbic dopamine neurons to modulate ‘wanting’ for food [21–23]. 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 [24]. The lower gut hormone PYY(3–36), which has now been convincingly demonstrated to suppress food intake in humans and rodents [25], also modulates activity of the ventral tegmental area (VTA) and ventral striatum [26].

On the other hand, ghrelin activates dopamine neurons in the VTA, increases dopamine turnover in the nucleus accumbens, and directly stimulates food intake when locally administered [27,28]. Since local ghrelin receptor blockade in the VTA blunted rebound feeding following fasting [27], these observations suggest that enhancement of reward processing in the mesolimbic dopamine system is an integral part of endogenous ghrelin’s orexigenic action.

In addition to circulating signals, neural signals carrying nutritionally relevant information originating from brainstem and hypothalamus can also modulate these cortico-limbic systems (Fig. 1). The best known example is gustatory information reaching the amygdala and insular cortex through relays in the NTS, parabrachial nucleus, and hypothalamus. Nutritionally relevant information from further down the alimentary canal mediated by vagal afferents closely follows gustatory pathways. The dense projections from the lateral hypothalamus to the entire cortical mantle and limbic structures, including orexin and MCH, have been reviewed before [1]. Orexin neurons, known to be activated by hypoglycemia, may augment food intake by their stimulation of dopamine neurons in the ventral tegmental area [29,30]. Orexin, together with galanin, enkephalin, and dynorphin, may also provide a paradoxical positive feedback

between circulating lipids and further stimulation of food intake [31). In addition, orexin projections to the olfactory bulb appear to modulate the sensitivity of peripheral olfactory processing. While leptin decreases, orexin increases the ability to smell potential food [5,32, 33].

In summary, it is clear that gut hormones and leptin do not only act on the energy balance control circuits in the hypothalamus and brainstem, but in addition impinge on cortico-limbic systems involved in cognitive, reward, and executive brain functions important for ingestive and exercise behavior, particularly in our modern environment. The studies with leptin are interpreted as additional, extrahypothalamic, evidence for its negative feedback action to regulate adiposity and body weight [21–23]. In keeping with the original adipostatic theory, they predict that under- and over-nutrition would increase and decrease, respectively, pleasure and reward from food, resulting in appropriate effects on food intake. The findings with ghrelin [9,27] suggest that an empty stomach enhances reward expectancy from food and the cognitive skills to find food.

Modulation of metabolic homeostatic regulation by cognitive and reward processes

Given these expanded negative feedback actions of leptin, why do increased leptin levels not prevent overconsumption of palatable foods and the development of obesity? The most plausible explanation might be that leptin has not evolved as a signal to prevent obesity. This model suggests that leptin's biological action happens only at low circulating levels, where its absence is a very strong survival signal to find and eat food, and normal levels merely stop this emergency mode but do little in preventing increases in adiposity. Mechanisms appear to have evolved to actively dampen the anorectic effects of supra-normal leptin levels as it may have conferred a disadvantage in a restrictive environment. In this view, leptin resistance does not represent pathological damage to the regulatory system, but instead is an appropriate physiological reaction to positive energy balance as suggested by leptin-resistance observed during pregnancy, old age, and during the long summer days of hibernators.

It is thus possible that the cognitive and rewarding brain actively interferes with safeguarding the upper adiposity limit by the hypothalamic regulator circuit. Clearly, the behavioral output of the two systems has to converge at some point in the neuraxis because they ultimately both affect food intake. Because the hypothalamus plays such a crucial role in the regulation of energy balance it is plausible that projections from the cognitive and rewarding brain to the hypothalamus might be involved.

There is an abundance of cortical inputs to the hypothalamus. The role of projections from the amygdala and prefrontal cortex to the lateral hypothalamus was examined in a rat model of conditioned food intake. Using a variation of the Weingarten protocol [34], rats were trained to associate a CS+ with the presentation of a food cup (UCS) during several training sessions, resulting in conditioned food intake even in the sated state. Elimination of the ventromedial prefrontal cortex or amydala-hypothalamus projections completely abolished conditioned food intake [35–37]. A functional network with direct projections from the amygdala and orbitomedial prefrontal cortex to the lateral hypothalamus was found to be crucial for this type of conditioned food intake to occur [38].

As discussed above, the nucleus accumbens is a key player in reward processing and it has direct projections to the hypothalamus. Furthermore, its chemical manipulation with the mu-opioid agonist DAMGO elicits voracious feeding of high-fat food in sated rats [39–41]. Based on these observations we hypothesized that accumbens-hypothalamus projections might engage the hypothalamic peptidergic systems known to be involved in metabolic appetite

control and that this might be an important pathway for the "cognitive" and "emotional" brain to override metabolic homeostatic regulation. We found that orexin-signaling in the ventral tegmental area is important for this reward-driven appetite to override metabolic repletion signals in pre-satiated rats. We further show that accumbens DAMGO in the absence of food selectively increases the proportion of orexin neurons expressing c-Fos in parts of the perifornical hypothalamus and that neural projections originating in DAMGO-responsive sites of the nucleus accumbens make close anatomical contacts with hypothalamic orexin neurons. These findings suggest that direct accumbens-hypothalamic projections can stimulate hypothalamic orexin neurons, which in turn through orexin1-receptor signaling in the ventral tegmental area and possibly other sites interfaces with the motivational and motor systems to increase intake of palatable food [42].

Because of their feed-forward character, certain cephalic phase responses could also be considered hedonistic mechanisms to temporarily neutralize and override metabolic feedback. The idea that during the initiation phase of ingestive behavior, seeing, smelling, and tasting, or the pure imagination of food (recall of stored representations), triggers the secretion of gastrointestinal and pancreatic hormones which, in turn, augment appetite is anchored in the anecdotal French saying: "l,appétit vient en mangeant" and has long been formulated in the ingestive behavior literature [43].

Lastly, neuroeconomics, a burgeoning new discipline of neuroscience, suggests that economic choice and decision-making may also ultimately control ingestive behavior, particularly in humans [44]. Specialized neurons in the orbitofrontal cortex of monkeys encode the value of offered and chosen goods such as food items independent of visuo-spatial factors and motor responses [45]. Furthermore, a delicate balance of activity within the left and right prefrontal cortex may be important for proper behavioral choice, as several lines of evidence suggest that damage to the right prefrontal cortex can cause a passion for eating and a specific preference for fine food [46].

Conclusions

The ability of metabolic signals to modulate brain circuits involved in the procurement of food and its reward value has been demonstrated in numerous studies in animals and humans. In starvation, these signals (or lack thereof) are not just powerful in triggering hypothalamic mechanisms of hyperphagia and energy efficiency, but also in putting the rest of the brain into a food procurement mood by mobilizing knowledge about the food environment and elevating food to the highest source of pleasure. However, when food is abundant and palatable, these signals are not able to prevent diet-induced hyperphagia and there is a *de facto* state of resistance to these signals in many obesity prone individuals. The most parsimonious explanation for this asymmetric response profile is that there was evolutionary pressure in the defense of starvation, but not in the defense of obesity, by these signals. If this is the case, one could say that the environmental pressures simply override the weak ability of the homeostatic system to defend the upper limit of body weight and adiposity.

It is too early to tell, which of the many interactions between metabolic and cognitive controls turn out to be crucially involved in the development of hyperphagia and obesity. Compared to the considerable advances made in hypothalamic control of energy balance over the past dozen years, we have just started to scratch the tip of the iceberg regarding the role of cortico-limbic systems and their interactions with the hypothalamus. With the advent of modern neuroimaging technology in humans, we should expect exciting new advances in this area soon.

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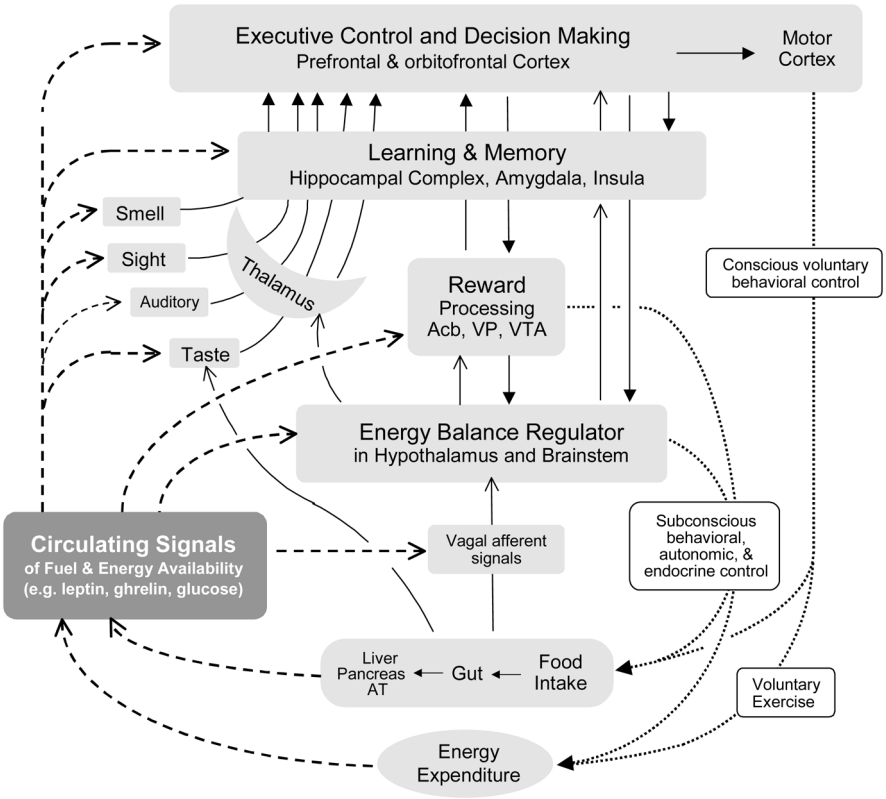

Fig. 1.

Schematic diagram showing the flow of information between components of the distributed neural system controlling food intake, energy expenditure, and energy homeostasis. The broken lines with open arrows on the left indicate modulation of sensory, cognitive, and reward processes by circulating signals of fuel availability, such as leptin, ghrelin, and glucose. The full lines/open arrows indicate modulation by nutritionally relevant neural signals such as taste and visceral sensory information, as well as signals originating from the hypothalamus. Full lines/closed arrows represent neural interconnections, and dotted lines/full arrows represent conscious and subconscious behavioral, autonomic, and endocrine output/effector pathways.