Eating for pleasure or calories
Huiyuan Zheng and Hans-Rudolf Berthoud

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 crosstalk 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.

Addresses
Neurobiology of Nutrition Laboratory, Pennington Biomedical Research Center, Louisiana State University System, 6400 Perkins Road, Baton Rouge, LA 70808, USA

Corresponding author: Berthoud, Hans-Rudolf (berthohr@pbrc.edu)

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 crucial 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 Figure 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 past 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 roles in energy intake and expenditure and the resulting energy balance. To acknowledge this apparent dichotomy, the terms ‘homeostatic’ and ‘nonhomeostatic’ 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 wild-type 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]. Although 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 expla-
nation 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
contrary, 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 crucially 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 long-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 (VTA) located in the midbrain and pro-
jecting through the mesolimbic dopamine system back to
the nucleus accumbens, the prefrontal cortex, the hippo-
campus, and amygdala. Nutritional relevant hormones
can modulate activity of the mesolimbic dopamine sys-
tem. Leptin and insulin can act directly on mesolimbic
dopamine neurons to modulate ‘wanting’ for food
[21**,22**,23]. Neural activity in the nucleus accumbens elicited by visual food stimuli is very high in genetically
leptin-deficient adolescents and promptly returns to nor-
mal levels upon leptin administration. Although 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 VTA and orbitofrontal cortex [26].

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

In addition to circulating signals, neural signals carrying
nutritionally relevant information originating from brain-
stem and hypothalamus can also modulate these cortico-
limbic systems (Figure 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
VTA [29,30]. Orexin, together with galanin, enkephalin,
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 per-
ipheral 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-nutrition and over-nutrition would increase and
decrease, respectively, pleasure and reward from food,
resulting in appropriate effects on food intake. The find-
ings 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 both ultimately affect food intake. It is plausible that projections from the cognitive and rewarding brain to the hypothalamus might be involved because the hypothalamus plays such a crucial role in the regulation of energy balance.

There is an abundance of cortical inputs to the hypothalamus. The role of projections from the amygdala and prefrontal cortex to the lateral hypothalamic 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 amygdala–hypothalamus projections completely abolished conditioned food intake [35*,36,37]. A functional network with direct projections from the amygdala and orbitomedial prefrontal cortex to the lateral hypothalamic 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 VTA is important for this reward-driven appetite to override metabolic repression signals in presatiated 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 VTA 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 temporally 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.

Acknowledgements
We would like to thank Christopher Morrison for discussions on homeostatic regulation and Laurel Patterson for editorial help. Supported by the National Institute of Health, Institute for Diabetes, Digestive and Kidney Diseases, DK47348 and DK071082.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
•• of outstanding interest


This paper reports that leptin-deficient mice find buried food 10 times faster than wild-type mice. Although the effect is normalized after leptin treatment, even high doses of leptin do not increase food-finding time beyond that of wild-type mice.


This paper reports that ghrelin has access to the hippocampus where it facilitates long-term potentiation and spatial memory. Impaired memory functions in the ghrelin-deficient mouse are rapidly reversed by ghrelin administration. This convincing demonstration of a role for ghrelin in learning and memory suggests that ghrelin may link the metabolic need state to higher brain functions.


In this paper, the author summarizes research suggesting that memory for recent eating may provide important restraint for subsequent eating and that this mechanism may be utilized by metabolic repletion signals to express satiety.


Microinjections of leptin or insulin into the ventral tegmental area abolish conditioned place preference. This is the first systematic analysis of modulation of reward functions by metabolic hormones.


Dopamine neurons in the ventral tegmental area thought to be crucial for ‘wanting’ are directly inhibited by leptin, resulting in decreased food intake. This is the first study using local leptin receptor knockdown to demonstrate increased food intake and preference for sweets.


Using fMRI, the authors demonstrate hyper-responsiveness of ventral striatal ‘wanting’ circuits to visual food stimuli that is instantly normalized upon leptin treatment. While in the leptin-deficient state, the response to see well-liked food is large after both fasting and refeeding, it is abolished after satiation in leptin-treated and normal individuals.


Using an impressive array of approaches, this is the first study demonstrating endogenous ghrelin stimulation of the mesolimbic dopamine system, suggesting that ghrelin’s appetitive stimulation depends partly on activating the ‘wanting’ system.


Based on a series of experiments, these authors show that Weingarten’s conditioned eating response in sated rats depends on a neural network comprising amygdala, ventromedial prefrontal cortex, and lateral hypothalamus.


This is the first study to show potential mechanism by which brain areas tracking reward can impinge on specific hypothalamic neurons that are part of the homeostatic regulator circuitry.


