In the course of evolution, the need to eat has powerfully shaped biological structure and function. As a result, nutrient-depletion signals strongly activate neural mechanisms that orchestrate foraging, appetitive, and ingestive behaviors and at the same time instigate an internal energy savings mode through autonomic, endocrine, and peripheral cellular mechanisms. Although the hypothalamus and brainstem play crucial roles in the initiation and coordination of these responses, it is the integrated action of a much more complex and distributed neural system that is engaged in this fundamental survival reflex. In our modern, media-driven and mechanized environment of plenty, it is particularly important to recognize the neural systems responsible for learning and memory, reward, emotions and mood, decision-making and choice, and dealing with stress. These neural systems appear to powerfully assist the hypothalamic regulator in defending the lower limits of body weight, but they do little in overcoming its inherent weakness to defend over-nutrition and the upper limits of body weight and adiposity. The challenge is to define the role of these extrahypothalamic brain structures involved in the cognitive, rewarding, and emotional aspects of ingestive and physical activity behaviors and their relationship to the homeostatic regulator, and to assess the capacity of these mechanisms in predisposing to obesity.

Key words: appetite, energy homeostasis, satiety, brain, gut hormones

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INTRODUCTION

Nutrients interact with the nervous system in many ways. Potential foods and food cues in the environment are perceived through visual, olfactory and auditory signals, and elicit nutrient-specific gustatory and retro-nasal olfactory signals at the very beginning of the ingestive process (Fig. 1). By comparing them against stored information from prior experience, these signals determine whether a particular food should be accepted or rejected. Ingestion of foods that were harmful in the past can thus be avoided as in conditioned food or taste aversion. On the other hand, ingestion, digestion, and metabolic assimilation of foods beneficial in the past is facilitated by the specific behavioral, autonomic, and endocrine responses elicited by these early sensory signals.1 These cephalic responses to desirable foods tend to further stimulate appetite in a feed-forward fashion, anecdotally known as the French saying “l’appetit vient en mangeant.”

Once ingested, food is first processed by the gastrointestinal tract, triggering a number of signals generated by mechano- and chemo-sensors. These signals inform the brain about the quantitative and qualitative aspects of incoming nutrients via primary afferent nerves and/or hormones (Fig. 1). This “gut-brain axis” has recently received much attention beyond its acknowledged function in the control of meal size,2 as some of the more recently discovered hormones such as glucagon-related peptide-1 (GLP-1) and polypeptide Y (PYY[3-36]) have the ability to suppress longer-term food intake and energy balance, making them attractive targets for drug development.

Absorbed nutrients impact the nervous system via two major mechanisms. Micronutrients and other specific compounds contained in foods can have profound effects on the structure and function of the nervous system in general—a rapidly emerging field of research referred to as “functional foods.” On the other hand, macronutrients entering the pathways of energy metabolism and storage interact with the nervous system directly or via the release of peptide hormones, allowing the brain to sense both the short- and long-term availability of fuels. Together with the behavioral, autonomic,
and endocrine output systems and integrative circuits of
the brain, these nutrient-sensing pathways form a homeo-
static system, which regulates energy balance through
the controls of intake and expenditure.

The function of this homeostatic energy balance sys-
tem is modulated or biased by other factors, notably circa-
dian and circannual rhythms, gender-related reproduc-
tive cycle, and relative stage of the life span. Lastly, all of
the above interactions of both environmental and internal
signals with the nervous system are sensitive to genetic pre-
disposition and possibly epigenetic modulation.

The major players and pathways in the neural con-
trol of food intake and energy balance are depicted in
Fig. 2. Three brain areas are of fundamental importance,
the caudal brainstem, the hypothalamus, and the cortico-
limbic system, with additional areas and connections
undoubtedly also involved. The three areas are bi-direc-
tionally interconnected and, to some extent, represent an
evolutionary hierarchy. The oldest, largely autonom-
ously functioning circuitry is contained in areas of the
dorsal and ventral medulla oblongata and the evolution-
arly most recent circuitry includes areas of the prefrontal
cortex predominantly under voluntary control.

BRAINSTEM CONTROLS OF SATIATION AND
MEAL SIZE

The caudal brainstem represents the oldest part of
the brain and is mainly concerned with vegetative func-
tions such as respiration and cardiovascular controls. It
also contains the complete pathways necessary for mas-
tication and swallowing, with all the accompanying au-
tonomic responses such as saliva secretion. Both mastication and deglutition are complex behaviors
that involve cooperation between large numbers of mus-
cles. Protection of the airways is of critical importance,
so that certain muscles cannot be activated indepen-
dently. Rhythmic, temporally fixed, and sequential pat-
terns of muscle action are therefore organized within
specialized pattern generator circuits.

Accepting beneficial food and rejecting potentially
harmful food are fundamental behaviors for an organism
to survive, and caudal brainstem areas play an essential
role in these processes. Gustatory input via taste receptor
cells on the tongue and palate and its primary represen-
tations in the rostral aspects of the nucleus tractus solitari-
tius (NTS) is considered most important for guiding
food intake and selection. The gustatory and trigeminal
systems act as gatekeepers at the entrance to the aliment-
ary canal. The classical four taste modalities represent
innate detectors for acceptable foods (sweet), dangerous
or toxic foods (bitter and sour), and special needs (salt,
water). There is now also increasing evidence for a taste
for fat, particularly polyunsaturated fatty acids.

In addition to taste, a wide spectrum of mechanosen-
sory, chemosensory, and thermosensory information
from the gastrointestinal tract and other abdominal or-
gans reaches the more caudal NTS and area postrema by
way of primary vagal afferent neurons and hormones.
Thus, ingested foods can signal many of their properties
to the caudal brainstem by sequential and parallel neural
and hormonal pathways. They include macronutrient
composition, caloric density, osmolarity, and potential
toxicity. Furthermore, the caudal brainstem receives in-

Figure 1. Overview of neurobiology of nutrition. Nutrient-related information from both the environment and the internal milieu can
influence the nervous system through a number of modes and pathways (broken arrows). In return, the nervous system can affect the
function of the nutrient-handling alimentary canal and organs involved in energy metabolism (full arrows).
formation about absorbed nutrients through sensors in the hepatic portal vein and liver, and the pancreas (as reviewed by Friedman 16).

Grill et al. 17,18 used a midbrain decerebrate rat model to examine the intrinsic capacity of the brainstem to orchestrate ingestive behavior in the absence of cross talk with the forebrain. In a series of studies using intraoral liquid food delivery, they documented an impressive catalog of integrative mechanisms complete within the brainstem, including discriminative responses to taste stimuli as expressed by acceptance or rejection responses,19 sympatho-adrenal counter-regulatory responses to glucoprivation,20 ingestive responses to insulin-induced hypoglycemia,21 sham feeding of sucrose solution,22 normal satiation,23 suppression of intraoral sucrose intake by CCK,24 and reduction of intake after a gastric preload.25 In addition, decerebrate rats confronted with the sucrose concentration contrast paradigm perform similar to intact rats, suggesting that the brainstem alone is sufficient to mediate complex reward-driven behavior that depends on a comparison process involving short-term memory.26 Like intact rats, decerebrate rats always licked more for a high than for a low concentration of sucrose when they were allowed to compare the two solutions during very brief access within the same daily session.

These observations demonstrate that the brainstem contains the complete basic neural circuitry to 1) orchestrate ingestion of food and fluid placed into the oral cavity, 2) generate most of the parasympathetic support accompanying the ingestive and digestive processes through the vagus nerve, 3) stop ingestion when the taste is aversive, when gastrointestinal feedback signals reach “satiety” levels, or when visceral sensors detect noxious or toxic stimuli, and 4) generate sympathetic responses related to severe energy depletion. Clearly, ingestive behavior and regulation of energy balance cannot occur without this circuitry.

However, decerebrate rats are incapable of other complex behaviors and autonomic adjustments necessary for the control of food intake and the regulation of energy balance. For one, decerebrate rats cannot voluntarily procure and consume meals. Furthermore, whereas intact rats respond to caloric restriction or deprivation with adaptive increases in food intake and a restoration of body weight, decerebrates fail to engage this adaptive homeostatic response. Therefore, while many of the fundamental processes involved in eating are embedded within the brainstem, higher areas are necessary for the display of adaptive behavior, particularly in a changing environment.

**HYPOTHALAMIC REGULATION OF ENERGY BALANCE**

Food intake is necessary to procure the energy, protein, and micronutrients necessary for life. It is thus not surprising that ingestive behavior is controlled by metabolic and nutritional status. While several brain areas play a role in this homeostatic system, a large body of data suggests that neurons within the hypothalamus are most critical. Research starting many decades ago and culminating in the last 10 years or so, suggests that populations of hypothalamic neurons sense the overall availability of nutrients directly or via hormones and then pass this information on to downstream neurons engaging behavioral, autonomic, and endocrine effectors and orchestrating a balanced response to maintain energy homeostasis.
Nutrient sensing in the arcuate nucleus

The arcuate nucleus of the hypothalamus (ARC) is a critical site for the integration of metabolic information (Fig. 4). Neurons within the ARC are sensitive to short- and long-term signals of nutritional status provided by circulating metabolites themselves, hormones, and neural inputs. Much of our understanding of how the hypothalamus influences energy homeostasis stems from work on leptin action within the ARC, although leptin is just one of many signals acting on ARC neurons and leptin also acts on sites outside the ARC. One population of leptin-sensitive neurons in the ARC expresses the potent orexigenic peptides Neuropeptide Y (NPY) and Agouti-related protein (AgRP). These NPY/AgRP neurons are primary drivers of food intake, as central injection of either NPY or AgRP leads to a profound increase in food intake. Although constitutive genetic knockout of either NPY or AgRP exerts only subtle effects on body weight regulation or leptin sensitivity, acute ablation of the NPY/AgRP neurons in adult animals leads to significant hypophagia and weight loss.27,28 Thus NPY/AgRP neurons play a significant role in the stimulation of feeding behavior, although other pathways can compensate for the loss of NPY and AgRP in early development.

Another population of ARC neurons expresses pro-opiomelanocortin (POMC) and cocaine and amphetamine regulated transcript (CART) (Fig. 4). POMC is a large precursor protein that is processed into a variety of smaller products, notably alpha-melanocyte stimulating hormone. Central injection of alpha-melanocyte stimulating hormone or its stable analog Melanotan II produces a marked suppression of food intake, while genetic deletion of POMC results in an obese phenotype.32,33 Thus NPY/AgRP neurons play a significant role in the stimulation of feeding behavior, although other pathways can compensate for the loss of NPY and AgRP in early development.

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These two neuron populations in the arcuate nucleus of the hypothalamus are critical integrators of metabolic and nutritional information, being sensitive to a number of signals conveying the availability of fuels that are 1) circulating in the plasma, 2) ready to be absorbed from the gastrointestinal tract, or 3) stored as glycogen or fat. Immediate availability of fuels is signaled by glucose, fatty acids, and amino acids, for which specific sensing mechanisms have been described in arcuate nucleus and other neurons of the hypothalamus.

Some neurons are sensitive to physiological variations in glucose concentrations,34 and these changes are mediated in part via signaling pathways similar to those mediating glucose-stimulated insulin secretion in pancreatic beta cells.35 The relevance of these pathways is evident from recent work demonstrating that deletion of hypothalamic GLUT236 or glucokinase37 induces significant increases in feeding behavior and hypothalamic gene expression, presumably by altering cellular energy status and/or AMP-kinase activity.38 ARC neurons also

Figure 3. Direct brainstem controls of food intake. Flow of sensory information from taste and gastrointestinal tract via the nucleus tractus solitarius to integrative areas in the medullary reticular formation and parabrachial complex, and to motor nuclei orchestrating the ingestive reflex. Descending modulation by hypothalamic and corticolimbic systems is indicated by broken arrows.
utilize defined signaling mechanisms to respond to fatty acids and amino acids, which both suppress food intake and alter peripheral glucose metabolism when administered into the brain ventricles.\textsuperscript{39–41} The ability of these molecules to alter neuronal function appears to be mediated by evolutionarily conserved nutrient sensing pathways such as AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR). These signaling molecules are acutely responsive to variations in cellular energy status; thus, it is not surprising that they also function within nutrient-sensing neurons.

Availability of fuels in the near future is signaled from the gut by gastrointestinal hormones such as Ghrelin, GLP-1, and PYY. Ghrelin stimulates NPY neurons through growth-hormone secretagogue receptors (GHS-R),\textsuperscript{42} while PYY(3-36) directly inhibits NPY neurons via Y2 autoreceptors.\textsuperscript{43} In addition, gut signals can influence the activity of neurons in the arcuate nucleus via ascending projections from the dorsal vagal complex.

Lastly, information about the level of energy stored in fat is signaled by circulating adiposity signals, particularly the hormones leptin and insulin. As mentioned above, both NPY/AgRP and POMC neurons express leptin receptors and are directly regulated by leptin. Selective deletion of leptin receptors within POMC neurons results in an obese phenotype,\textsuperscript{44} although the effect is much less robust than loss of POMC or deletion of leptin receptors in all neurons. Leptin acts on NPY/AgRP and POMC neurons in an opposing fashion, inhibiting NPY/AgRP neurons while stimulating POMC neurons. Thus, while low leptin levels result in a profound stimulation of food intake and suppression of energy expenditure, high leptin levels result in suppression of food intake and stimulation of energy expenditure. Similar evidence exists demonstrating that insulin acts as an adiposity signal to the brain. Injection of insulin directly into the brain suppresses food intake and regulates POMC and NPY/AgRP neurons in a manner similar to leptin,\textsuperscript{45} while genetic or pharmacological inhibition of insulin action within the brain enhances food intake and weight, suggesting that brain insulin action is necessary for appropriate regulation of body weight.

**Molecular integration of metabolic information**

While it is clear that hypothalamic neurons sense and respond to a variety of circulating nutritional signals, the intracellular signaling pathways that mediate and integrate these responses are only now being defined. It becomes apparent that the richness of these intracellular signaling cascades and their coupling to changes in neuronal excitability, peptide expression, and synaptic connectivity, may provide the major substrate for integrative processes, providing new possibilities for the development of pharmacological and behavioral tools in the fight against obesity.

Two of the most exciting new players in intraneuronal integration are AMP-activated kinase (AMPK) and mammalian target of rapamycin (mTOR). AMPK is an evolutionarily conserved serine-threonine kinase that responds to changes in cellular energy levels,\textsuperscript{46} AMPK is sensitive to the AMP/ATP ratio, such that depletion of...
cellular energy stores activates AMPK signaling. While activation of AMPK in peripheral tissues leads to rigorous defense of cellular energy availability through increased oxidation, AMPK activation in the arcuate nucleus increases food intake and energy conservation.\textsuperscript{47} Recent work has indicated that AMPK is sensitive to levels of circulating nutrients and hormones, and may represent a common mediator of their effects. As an example, both glucose and leptin acutely inhibit hypothalamic AMPK activity, and activation of AMPK prevents both glucose and leptin-dependent changes in food intake.\textsuperscript{47,48} Thus, while glucose and leptin represent very different nutritional signals and initially engage different intracellular signaling pathways, AMPK appears to contribute to the hypothalamic actions of both signals. Taken together, these observations provide strong support for the capacity of AMPK to integrate information from these multiple hormone and nutrient signaling pathways and to play a key role in the hypothalamic regulation of food intake and energy balance.

Mammalian target of rapamycin is another evolutionarily conserved energy sensor that has assumed a specific functional role in hypothalamic regulation of energy balance.\textsuperscript{40} In many peripheral tissues, mTOR plays a key role in coupling cellular energy status and growth factor signaling to protein synthesis, growth and division. mTOR is expressed within key populations of mediobasal hypothalamic neurons that are sensitive to amino acid availability. The ability of amino acids to suppress food intake and regulate neuropeptide expression depends on mTOR.\textsuperscript{40,49} Leptin may also regulate mTOR, indicating that multiple signals of nutritional status converge on mTOR signaling within the hypothalamus.\textsuperscript{40}

**Linking nutrient sensing to energy balance effector systems**

The ability of ARC neurons to regulate food intake is dependent on downstream neuronal targets. These downstream neurons are thus second-order targets, and exist in many areas both within and outside the hypothalamus (Fig. 4). The major recipients of arcuate input are other hypothalamic areas, in particular the paraventricular nucleus (PVN) and lateral/perifornical hypothalamic areas (LHA). These two brain regions are classically associated with the regulation of food intake and autonomic output, and each contains a variety of neuropeptides associated with energy balance control. Metabolic information encoded by differential input from NPY/AgRP and POMC/CART neurons is integrated with additional nutrient sensing capabilities within these second-order downstream neurons and with neuronal input from additional brain areas. These second-order neurons, in turn, project widely to third- and higher-order neurons located in many areas of the brain and spinal cord.\textsuperscript{50}

The lateral/perifornical hypothalamus provides a compelling example of this interconnection and integration (as reviewed by Berthoud\textsuperscript{50}). LHA neurons are classically associated with feeding behavior, and electrical stimulation of the LHA produces a rapid and profound induction of feeding that ends immediately upon cessation of the stimulation. Neurons within the LHA contain several “feeding” peptides such as hypocretin/orxen, melanin-concentrating hormone, neotensin, and histamine, and many of these neurons receive direct input from ARC NPY/AgRP and POMC neurons. In addition to this metabolic information, the LHA also receives information from brain areas associated with reward, motivation, learning, and memory (orbitofrontal cortex, nucleus accumbens, amygdala, ventral tegmental area), from areas associated with sensory input (insular and olfactory cortex), and from brainstem areas associated with vagal and visceral sensory input, sensory motor coordination, and arousal (NTS, parabrachial nucleus, locus coeruleus) (see Berthoud\textsuperscript{50} for review). While the role that many of these specific connections play is unclear, the consensus is that the LHA is receiving input from a wide variety of areas in addition to ARC-derived metabolic information. In turn, the LHA projects widely through the entire brain,\textsuperscript{50} from the cortex to the spinal cord. Consequently, information processed within the LHA has the capacity to impact nearly every neural activity.

Similarly, the paraventricular nucleus (PVN) also represents a downstream target of ARC neurons that receives information from and projections to a variety of locations. In particular, the PVN is classically associated with neuroendocrine function via the hypothalamic pituitary axis, as well as a regulation of the autonomic nervous system. For example, TRH neurons receive direct input from ARC neurons, and their opposing regulation of the TRH neuron contributes to the metabolic regulation of the thyroid axis and thus metabolism.\textsuperscript{51} Thus, ARC-derived metabolic information has the capacity to influence a variety of behavioral endpoints via the LHA, as well as neuroendocrine and autonomic endpoints via the PVN.

In addition, ARC neurons project to areas other than the PVN and LHA. For example, leptin-sensitive POMC neurons project directly to brainstem areas associated with the response to satiety signals and autonomic outflow.\textsuperscript{52,53} The reciprocal relationship between areas in the brainstem and hypothalamus is particularly important for understanding the coordination between food intake and autonomic nervous system activity. This issue has been addressed in several recent reviews.\textsuperscript{18,54,55}
Taken together, available evidence indicates that the metabolic information from arcuate nucleus neurons is integrated into a neural network that is also receiving input from and providing input to a variety of additional brain areas. This network is therefore positioned to modulate an array of neuronal processes that each play a critical role in the regulation of feeding behavior, autonomic outflow, neuroendocrine function, and more cognitive aspects such as reward, learning and memory.

COGNITIVE AND EMOTIONAL CONTROLS OF APPETITE

The metabolic controls of eating discussed above are embedded in a much larger neural system allowing animals and humans to interact with the food-providing environment. In the mostly restrictive environments of the past, evolutionary pressures forged the development of neural systems that made it easy to locate, secure, store, preserve, prepare, and cook high-quality foods, and to pass valuable experience with these activities on to offspring. These activities require neural functions that are very different from the ones involved in managing the internal milieu, but they are powerfully influenced by the metabolic state. Although these neural systems and functions are used for most other behaviors, the need to procure and eat food must have undoubtedly shaped their phylogenetic development.

The following discussion focuses on the basic neural mechanisms and systems involved in the interaction with the food environment, first highlighting the elaborate sensory and cognitive mechanisms necessary for successful foraging and food procurement and then the concepts and potential neural substrates of reward, liking, and wanting and their collective role in ingestive behavior.

Foraging and procurement

Procurement of food and water is one of the most important behaviors for any life form. Even primitive invertebrates such as insects use elaborate navigation and communication strategies to secure food sources and guarantee survival. An example is the honey bee, which engages in an elaborate dance to communicate the location and abundance of a food source to other worker bees in the hive. It is truly remarkable that the honey bee with its relatively small brain is able to generate such a complex memory, encode the salient information into dance movements and, in the reverse, lay down a working memory from watching the dance and use it to find the food source—and all this not for immediate personal reward, but for the future benefit of the bee society. Ants use similarly elaborate communication skills to teach each other how to find food on their long journeys along the forest floor. These examples illustrate that, even in simple organisms, large portions of the nervous system are dedicated to the procurement of food. It should not be surprising that the huge cortex of modern humans harbors an extraordinary ability to deal with the procurement of food.

Representations of experience with foods

Memorial representations of foods and food cues are available to the foraging human long before food is actually seen, smelled, or tasted. Humans and animals vividly recall places and events associated with the consumption of pleasant foods, as well as experiences associated with unpleasant foods. 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 cortex, which is part of the prefrontal cortex, and perhaps the amygdala. These areas receive converging information through all sensory modalities; thus, representations contain any number of sensory attributes, including shape, color, taste, and flavor, as well as links to time, location, and social context (see bee example above). Furthermore, links to significant (positive or negative) consequences of ingestion of the food, its reward value, can also be bundled into the same representations.

Olfactory information is relayed through the olfactory bulb and primary olfactory cortex (consisting of mainly piriform cortex) to the orbitofrontal cortex. Odor molecules are detected by a large number of receptor cells in the olfactory epithelium that each project to glomeruli in the olfactory bulb. In the mouse, there are about 1000 and in primates about 350 genes encoding different receptor proteins. Odor stimuli produce specific spatial patterns of activity, so-called "odor images" or "odor maps" across the olfactory bulb. In the mouse, these images are actually seen, smelled, or tasted. Humans and animals available to the foraging human long before food is actually seen, smelled, or tasted. Humans and animals vividly recall places and events associated with the consumption of pleasant foods, as well as experiences associated with unpleasant foods. 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 cortex, which is part of the prefrontal cortex, and perhaps the amygdala. These areas receive converging information through all sensory modalities; thus, representations contain any number of sensory attributes, including shape, color, taste, and flavor, as well as links to time, location, and social context (see bee example above). Furthermore, links to significant (positive or negative) consequences of ingestion of the food, its reward value, can also be bundled into the same representations.

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Visual and auditory information are also relayed via their respective thalamic relays to the orbitofrontal cortex. Visual information plays a key role in the recognition of potential foods, particularly when it is serving as a cue in the form of a picture or image in the absence of smell and taste, for example, on the television screen.

Gustatory and viscerosensitive information reaches
the orbitofrontal cortex via relays in the solitary nucleus, thalamus, and insular cortex. In addition, metabolic information from circulating fuels and hormones can potentially reach the orbitofrontal cortex via sensors in the caudal medulla and hypothalamus as discussed in the previous section. Information from mediobasal hypothalamic nutrient sensors is relayed to the lateral hypothalamus, which has profuse projections to most of the cortex.

Finally, somatosensory information, particularly from the oral cavity, also reaches the orbitofrontal cortex via the thalamus and somatosensory cortex (see review by Verhagen). It includes the sensations of fine touch (creaminess), deep pressure (crunchiness), temperature and pain (burning sensation of hot chili pepper), and astringency (e.g. dry wine), which are major determinants for the palatability of everyday foods and criteria for the development of commercial foods.

It is apparent from the above discussion that the orbitofrontal cortex is a site of convergence for all sensory information. In the orbitofrontal cortex, sensory representations of experience, which can be recalled to influence future choices and to predict where food may be most likely acquired. Of course, the orbitofrontal cortex does not work in isolation; it 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 (see review by Verhagen). It is within these areas that multimodal representations of experience with foods are thought to be available as working memory for constant updating, not unlike the RAM (random access memory) space on a computer. Recent investigations into the morphology and function of cortical columns, the basic building block of the human cortex, suggest that synaptic contacts between neurons in the various cortical layers are in constant flux, with new synapses forming and existing synapses disappearing either spontaneously or induced by neural excitation.

Learning about foods: conditioned food intake and aversion

Dealing with food in the environment requires the distinction and recall of foods that are beneficial and those that are harmful. Most, but not all, of this knowledge is acquired through learning processes. As discussed above, neural representations of experience with particular foods together with environmental and social context information are available in working memory in the orbitofrontal cortex and may be stored in the hippocampal formation more permanently. Non-invasive imaging techniques have clearly demonstrated that simply thinking about food can modulate neural activity in specific brain areas known to be involved in the cogni-
tive controls of appetitive behaviors and lead to physiological responses such as saliva, gastric acid, and insulin secretion. Even in the absence of real food, food cues that have been previously linked to specific foods can serve as conditioned stimuli to recall their memorial representations.

Lesion experiments in rats suggest different but complimentary roles for the orbitofrontal cortex and basomedial amygdala in learning about representations of specific experiences with food and using them to guide appetitive behavior. It has long been demonstrated that food intake can be conditioned over time by repeatedly pairing the presentation of food with a tone or light (CS+) in hungry rats. After learning this task, even sated rats will approach and consume food upon exposure to the CS+. When the reinforcer (food) in this Pavlovian conditioning task is later devalued by pairing it with an aversive agent (LiCl), rats will exhibit reduced approach behavior to the food cup (conditioned response). If excitotoxic lesions of the orbitofrontal cortex or basolateral amygdala are placed before learning the conditioned task, then rats learn the task but no longer exhibit the reduced approach behavior after LiCl devaluation. However, if the lesions are placed after learning the conditioned task, lesions in the orbitofrontal cortex, but not the basolateral amygdala, result in loss of the devaluation-induced reduction in approach behavior. These observations suggest that the basolateral amygdala is critical to learning representations that link cues to the incentive properties of outcomes, but not for maintaining such representations. In contrast, the orbitofrontal cortex seems to be critical for maintaining memorial representations that link cues to the incentive properties of outcomes, for updating them with new information, and for using them to guide appetitive behavior.

Imaging studies in human subjects point to the same cortical areas for encoding the predictive reward value of olfactory cues. For example, hungry subjects scanned during learning and anticipation of food-based olfactory rewards exhibit neural responses in the insular and orbitofrontal cortices and in the amygdala. Together with other neuroimaging studies, these observations point to the prefrontal/orbitofrontal cortex and amygdala as playing crucial roles in dealing with the acquisition, storage, and recall of representations of experience with food.

Representations of experience with food are not only important for the procurement process. Because they contain an emotional component, they are also important for the determination of the subjective value we assign to a particular food. These conditioning and learning mechanisms are exploited by the advertisement industry. It is well known to shopping mothers that television significantly influences a child’s valuation of certain food items, and similar influences are undoubtedly active in the food choices of adults. The power of culturally based brand images to influence behavioral choices through measurable changes in neural activity has been recently demonstrated in a human imaging study.

Affective controls of food intake: neural correlates of ‘liking’ and ‘wanting’

Emotions may have evolved to make animals engage in behaviors with a beneficial outcome and to avoid engaging in behaviors that potentially diminish survival. Applied to nutrition, tasting physiologically beneficial foods elicits a feeling of pleasure, while tasting bitter, potentially toxic, foods elicits negative emotions. Although the neural pathways necessary for taste perception are well described, the mechanisms by which the rewarding effects of pleasurable tastes and flavors guide intake are less well understood.

Berridge and Robinson have outlined the potential psychological components that constitute reward into learning, liking, and wanting, and have outlined the major brain structures most likely involved. Areas within the hindbrain clearly contribute to the perception of the rewarding value of foods. The characteristic orofacial expressions displayed by decerebrate rats and anencephalic infants in response to sweet taste strongly suggests that the hindbrain is sufficient to mediate the hedonic impact of pleasant stimuli. Berridge and Robinson refer to these expressions as objective affective reactions or implicit affect, and to the psychological process as ‘liking.’

Besides neural circuits in the hindbrain, the nucleus accumbens and ventral pallidum in the limbic forebrain are other key components of the distributed neural network mediating ‘liking’ of palatable foods (Fig. 5). The mu-opioid receptor appears to play a crucial role. Local injection of the selective mu-opioid agonist DAMGO into the nucleus accumbens elicits voracious food intake, particularly of palatable sweet or high-fat foods. This increased consumption of highly palatable foods appears to be due to increased ‘liking’, as morphine microinjections into this area increased the number of positive affective reactions, and microinjection of a selective mu-opioid antagonist reduced sucrose drinking. Based on the resulting c-Fos plumes, the most sensitive area for this effect was the caudal shell of the nucleus accumbens, near the border with the adjacent core.

To consciously experience and give subjective ratings of pleasure from palatable foods (liking), humans appear to also use areas in the prefrontal and cingulate cortex. The neurological substrate responsible for experiencing pleasure from food is complex and distributed.
throughout the neuraxis and cannot be conveniently eliminated by tissue lesions. One of the common denominators of the distributed network may be opioiergic transmission, particularly through the mu-opioid receptor. However, chronic treatment with the non-selective opioid receptor antagonist naloxone, while clearly curbing intake of palatable foods, has not resulted in significant changes of energy balance. The mu-opioid receptor-deficient mouse showed some resistance to diet-induced obesity, but the effect was apparently not mediated by changes in food intake. Newer, more selective opioid antagonists currently tested in rats may be more promising. Another possible denominator of the distributed pleasure network may be signaling through the CB1 cannabinoid receptor, which is distributed throughout most of the components of the network. Like opioids, endocannabinoids signaling through the CB1-receptor may also selectively suppress appetite for palatable foods.

The other psychological process involved in reward is motivation, incentive salience, or ‘wanting,’ as termed by Berridge and Robinson. Although ‘liking’ a food is typically followed by ‘wanting’ and eating it, ‘wanting’ is a dissociable process that has a distinct underlying neural substrate. This distinction grew mainly out of research on drug addiction, where stimuli that are often no longer ‘liked’ are still intensely ‘wanted’. Just as learning and ‘liking’ do, motivation has a conscious or explicit and an unconscious or implicit aspect.

As stated by Berridge and Robinson, “wanting or incentive salience is a motivational, rather than an affective, component of reward. Its attribution transforms mere sensory information about rewards and their cues (sights, sounds and smells) into attractive, desired, riveting incentives” (Berridge and Robinson p. 510). Contrary to the long-held view, the mesolimbic dopamine system does not play any role in the affect or ‘liking’ of pleasurable stimuli, recent evidence instead indicates that the mesolimbic dopamine system is crucial for the mobilization of motor behavior to obtain pleasurable stimuli, termed ‘wanting’ by Berridge and Robinson. Dopaminergic projections from the ventral tegmental area to the nucleus accumbens and prefrontal cortex are the most crucial component of the implicit or unconscious ‘wanting’ system (Fig. 5). Manipulation of this dopamine system powerfully influences ‘wanting’ (instrumental performance for and consumption of) drugs or food, but not ‘liking’. The lateral hypothalamus is also involved in ‘wanting’ as electrical stimulation of this area induces rats to vigorously self-stimulate and eat (‘want’) food, even though it does not make them ‘like’ the food more.

The mesolimbic ‘wanting’ system is intimately connected with elements of the ‘metabolic’ regulatory system mentioned previously. Caloric restriction alters the incentive value of foods and drugs, such that the restricted or food-deprived animal ‘wants’ these stimuli more fervently than the sated animal. Leptin and insulin appear to contribute to this effect, as both attenuate the incentive value of food and drugs and alter behavior in a manner consistent with a reduction in the ‘wanting’ of food. The mechanisms underlying these effects are currently unclear. While it is likely that this metabolic drive is at least partly transmitted via the hypothalamic systems mentioned earlier, available evidence also indicates that leptin and insulin act directly on mesolimbic dopamine neurons to modulate ‘wanting’ for food. Leptin can also indirectly modulate mesolimbic dopamine neurons via action on lateral hypothalamic orexin and neurotensin neurons with projections to the ventral tegmental area.

WHY IS OBESITY INCREASING?

Feeding behavior and, ultimately, energy balance are clearly controlled by complex neural systems, imposing on many brain areas. In this overall control system, brainstem and hypothalamic circuits involved in the regulatory feedback loop of energy availability are intimately linked to higher areas of the brain involved in learning and memory, affect and emotion. Obesity could theoretically result from any pathological malfunction or from lack of adaptation of any components of this system to a changing environment (Fig. 6). Most of the research aimed at identifying pathological defects is directed towards a rather limited part of the overall control system, namely the feedback mechanisms linking the internal state to the controls of food intake and energy expenditure, as exemplified by leptin effects on specific neuron populations in the hypothalamus and brainstem. It is clear, however, that defects in other parts, namely the cognitive and affective controls could just as well lead to the development of obesity, but very little effort has been directed towards this topic. Therefore, we would like to focus on two major candidate mechanisms for the cause of obesity, 1) inadequate sensing of ingested nutrients due to defective feedback mechanisms and 2) over-stimulation of reward mechanisms combined with an increasingly sedentary lifestyle, due to environmental pressures.

Defects in feedback signaling from the internal milieu: the case of leptin resistance

When signals informing the brain about the availability of nutrients are either not produced or lose their capacity to modulate energy balance effectors, either starvation or obesity results. This is best illustrated by the
extreme obesity resulting from defects in leptin-production, which can be rapidly reversed by leptin treatment in mice and humans.\textsuperscript{119,120} There is a host of other feedback signals whose defective signaling to the brain and within their downstream effector pathways has been implicated in the development of obesity, such as the hormones insulin,\textsuperscript{121} PYY[3-36] and GLP-1,\textsuperscript{122} ghrelin,\textsuperscript{123} and the metabolites glucose,\textsuperscript{36} amino acids, and fatty acids.\textsuperscript{40,41} Here, we will focus on the leptin-signaling system for which there is the most experimental evidence available to date.

In most obese humans, plasma leptin levels are appropriately high for the degree of adiposity, indicating there is nothing wrong with leptin production but there is a state of resistance within the leptin-signaling pathway. The causes of leptin resistance could be genetic, epigenetic, or acquired during early life (imprinting) or later in life, or any combination thereof. An example of a genetic cause is illustrated by the occurrence of obesity in humans with point mutations in the MC4-receptor gene, leading to alterations in melanocortin signaling, which is one of the key effector pathways for leptin.\textsuperscript{124} It is obvious that monogenic leptin resistance is permanent and can only be remedied by gene therapy or pharmacological intervention downstream of blockage. However, the frequency of such mutations is low and it is highly unlikely that it increased significantly within the last 20 years or so, the time span during which the prevalence of obesity more than doubled. This leaves polygenic and/or acquired differences as the most likely determinants of leptin resistance. Data from polygenic animal models indicate that rats bred selectively for their increased adiposity when exposed to a high-fat diet (DIO or obesity-prone rats) display reduced sensitivity to central insulin even prior to exposure to a high-fat diet;\textsuperscript{125} suggesting that genetic variations in insulin and leptin sensitivity may underlie the variable susceptibility to obesity.

Epigenetic and non-genetic (acquired) mechanisms are increasingly recognized as potential causes of common human obesity.\textsuperscript{126} Perinatal imprinting could potentially cause leptin resistance and other malfunctions contributing to the so-called metabolic syndrome later in life.\textsuperscript{127,128} This theory suggests that early life events such as malnutrition in utero shape the regulatory mechanisms in such a fashion that the insult, if continued, has a minimal impact in later life. Specifically, maternal undernutrition would render the regulatory system more fuel-efficient, resulting in optimal energy homeostasis later in life as long as the restrictive conditions continue. The problem arises when the environmental conditions later in life do not match the ones prevailing during the imprinting period. Given the rapid increases in availability, energy density, and palatability of food in the last 20 years, this mechanism could also potentially play a role in the recent increase of obesity in the industrialized world.

Susceptibility to leptin resistance could well be co-determined by early life events and genetic predisposition, coming to fruition when there is a mismatch in environment, such as in modern humans, mice, and rats on a high-fat diet,\textsuperscript{129} cats and dogs fed today’s palatable foods, and in bears and baboons eating from garbage cans.\textsuperscript{130,131} In mice it has been shown that leptin resistance and obesity induced by a high-fat diet occurred in a subpopulation of a genetically inbred strain, suggesting that epigenetic or non-genetic mechanisms are sufficient.\textsuperscript{129}

While the phenomenon of leptin resistance has clearly been documented in obese animals and humans,
the site within its signaling pathway and the mechanism(s) of its induction are currently unclear. One intriguing possibility is that high-fat diets produce alterations in the blood-brain barrier, such that leptin is less capable of accessing brain areas regulating food intake. A putative mechanism for reduced leptin transport is the increase in triglycerides that occur in response to high-fat feeding. An alternative explanation is that elevated triglycerides signal dependence on milk ingestion after birth, a time when food intake can hardly be too high and there is no need for satiety signaling by leptin. This would fit the observation that the blockade of leptin transport through the blood-brain barrier is specific to milk triglycerides. The thought that the obesity crisis might be caused by a case of “mistaken identity” is puzzling and requires careful further testing.

In addition to reduced BBB transport, obese individuals also display a clear reduction in the capacity of critical hypothalamic circuits to respond to leptin. As discussed in detail above, leptin engages multiple intracellular signaling pathways to regulate feeding-relevant neurons. Like most signaling cascades, these pathways are both negatively and positively regulated, and suppression of positive or induction of negative regulators of leptin signaling has been suggested as a potential mechanism for leptin resistance. Neuron-specific deletion of two negative regulators, suppressor of cytokine signaling 3 (SOCS-3) or protein tyrosine phosphatase 1B (PTP1B), protects mice from developing leptin resistance, hyperphagia, and dietary obesity, and PTP1B contributes to leptin resistance with age. These observations demonstrate that interventions enhancing central leptin sensitivity can protect against obesity and provide an interesting target for the development of pharmacological tools.

Although available evidence indicates that reductions in hypothalamic leptin sensitivity contribute to obesity, in many cases this leptin resistance appears to be reversible. In hibernators, leptin resistance turns on and off during periods of weight gain or loss, suggesting that the ability to stimulate or suppress leptin signaling is a normal physiological property of these critical neurons. Based on these observations, it is possible to regard leptin resistance not as a pathological failure of the system, but instead as an appropriate response to allow animals to gain weight for future energy needs. The modern human environment could thus be regarded as the equivalent of continuous “summer” associated with leptin resistance. Before the modern era, this summer would be broken by winter or other periods of scarcer food supply 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. Moreover, leptin resistance does not only result from high-fat feeding; it is also induced by additional conditions such as age or pregnancy and prolonged receptor stimulation by exogenously administered leptin. The fact that diet-induced leptin resistance in genetically identical mice is fully reversible by putting animals back on normal chow diet further supports the natural reversibility of this system.

Thus, an alternative explanation for leptin resistance is that leptin has not evolved as a signal to prevent obesity. This model suggests that leptin is biologically relevant mainly at low circulating levels, with its absence being a very strong signal to find and eat food and conserve energy in order to survive. Normal levels merely stop this emergency mode while doing relatively little in preventing increases in adiposity. Mechanisms to actively dampen the anorectic effects of higher leptin levels may have evolved to confer an advantage in a restrictive environment. This model would propose that leptin resistance does not represent pathological damage to the regulatory system, but instead is an adaptive physiological response to changing environmental conditions.

**Environmental pressures on energy balance: super-sizing of energy-dense and palatable foods and sedentary lifestyle**

Most rodent species are susceptible to diet-induced obesity, and the changes in food intake and body weight in rats given access to a variety of palatable foods are striking. This “cafeteria” diet is very similar to the diet many modern humans are faced with every day. Availability, portion size, energy density, variety, and palatability have been identified as the major factors determining increased energy intake in humans and rodents (Fig. 6).

An equally important factor contributing to the obesity epidemic seems to be the lack of physical activity. Although these combined environmental pressures are assumed by many to be the primary cause of obesity, the supporting evidence is often indirect, particularly in human studies where well-controlled long-term interventional studies are still difficult to conduct.

One of the fundamental questions is how obesity driven by such environmental factors can develop in the face of a normally operating homeostatic system. Apparently, the energy imbalance caused by such factors is not, or only weakly, counteracted by the homeostatic regulatory system. Given that at least parts of the reward system are subject to negative feedback control by the
availability of endogenous nutrients such as leptin and insulin, the strong and sustained response to palatable diets is surprising. This is, unless the same rapid resistance to these feedback signals develops in reward circuits, as it does in the hypothalamus (see discussion above). Few studies have addressed this important question. In one study, diet-induced leptin resistance was limited to the arcuate nucleus, with other hypothalamic and extra-hypothalamic leptin receptors retaining sensitivity. If leptin sensitivity in reward circuits would not be compromised by palatable diets, and increased consumption would continue even in the presence of elevated leptin levels commensurate with the developing obesity, one would have to conclude that the effectiveness of leptin to curb reward is low. Maybe the major function of leptin in these circuits is to heighten reward when food is scarce and not very palatable and not to curtail reward when food is plenty. In addition to increased palatability, availability, in terms of both access to prepared foods and large portion sizes, is an important factor for increased consumption. The neural systems underlying changes in intake induced by availability and how they interact with other systems are poorly understood and deserve attention.

Clearly, experimental evidence supporting a role for reward is not as strong as that for the homeostatic regulatory system. While critical lesions in the homeostatic control system result in rapid development of robust obesity, and manipulations maintaining leptin-sensitivity result in resistance to diet-induced obesity, experimental manipulations aimed at the cognitive and reward systems have not yet been demonstrated to produce similarly strong effects on energy balance.

CONCLUSIONS

Significant progress has been made in identifying the neural mechanisms involved in the controls of ingestive behavior and energy balance. The hypothalamus has been confirmed as a crucial node in the homeostatic regulatory system. In addition, important roles for the reciprocal gut-brain communication pathways are emerging, and the neural organization of cross talk between hypothalamus and brainstem is beginning to be better defined. Within the hypothalamus, there is a new appreciation for the highly complex intracellular signaling pathways that serve to integrate the numerous nutrient, hormonal, and neural signals informing the brain about the internal milieu.

Yet despite this progress, the prevalence of obesity is increasing at an alarming pace in genetically predisposed segments of the global population. While it is clear that the cause of this obesity epidemic has to be found in the rapid changes in environment and lifestyle, it is far from clear what specific neural systems and mechanisms are affected by these changes and why the homeostatic regulation breaks down. Because food-related signals and cues from the external world interact primarily with the cognitive and emotional brain, it will be important to study the underlying neural mechanisms and pathways with the same vigor and sophisticated tools as have been applied to the hypothalamic homeostatic regulation. In fact, it is artificial to distinguish homeostatic from non-homeostatic mechanisms, as recent findings show that the cognitive, emotional, and rewarding brain is intimately linked to the internal metabolic regulatory systems.

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