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Hans-Rudolf Berthoud, Natalie R. Lenard, and Andrew C. Shin

Neurobiology of Nutrition Laboratory, Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, Louisiana

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Berthoud HR, Lenard NR, Shin AC. Food reward, hyperphagia, and obesity. *Am J Physiol Regul Integr Comp Physiol* 300: R1266–R1277, 2011. First published March 16, 2011; doi:10.1152/ajpregu.00028.2011.—Given the unabated obesity problem, there is increasing appreciation of expressions like "my eyes are bigger than my stomach," and recent studies in rodents and humans suggest that dysregulated brain reward pathways may be contributing not only to drug addiction but also to increased intake of palatable foods and ultimately obesity. After describing recent progress in revealing the neural pathways and mechanisms underlying food reward and the attribution of incentive salience by internal state signals, we analyze the potentially circular relationship between palatable food intake, hyperphagia, and obesity. Are there preexisting individual differences in reward functions at an early age, and could they be responsible for development of obesity later in life? Does repeated exposure to palatable foods set off a cascade of sensitization as in drug and alcohol addiction? Are reward functions altered by secondary effects of the obese state, such as increased signaling through inflammatory, oxidative, and mitochondrial stress pathways? Answering these questions will significantly impact prevention and treatment of obesity and its ensuing comorbidities as well as eating disorders and drug and alcohol addiction.

palatability; food addiction; liking; wanting; motivation; reinforcement; neuroimaging; leptin; insulin; body weight; weight loss

THE CURRENT OBESITY EPIDEMIC is best explained as a mismatch between the modern environment/lifestyle and biological response patterns that evolved in a scarce environment. Biological traits like strong attraction to food and food cues, slow satiety mechanisms, and high metabolic efficiency, advantageous for survival in a scarce environment, seem now to be our worst enemies when it comes to resisting an abundance of food (130, 169). Food intake and energy expenditure are thought to be controlled by complex, redundant, and distributed neural systems, likely involving thousands of genes and reflecting the fundamental biological importance of adequate nutrient supply and energy balance (15, 103). There has been much progress in identifying the important role of the hypothalamus and areas in the brainstem in the various hormonal and neural mechanisms by which the brain informs itself about availability of ingested and stored nutrients and, in turn, generates behavioral, autonomic, and endocrine output (54, 149) (Fig. 1). Some of the genes involved in this homeostatic regulator are crucial for energy balance as manifested in the well-known monogenic obesity models such as leptin-deficiency (58). However, it can be clearly demonstrated that much larger portions of the nervous system of animals and humans, including cortex, basal ganglia, and the limbic system, are concerned with the procurement of food as a basic and evolutionarily conserved survival mechanism to defend body weight (146). By forming representations and reward expectancies through processes of learning and memory, these systems likely evolved to engage powerful motivations and drives for guaranteed supply with and ingestion of beneficial foods from a sparse and often hostile environment. Now these systems are simply overwhelmed with an abundance of food and food cues that are no longer contested by predators and interrupted by famines (168). Regrettably, the anatomy, chemistry, and functions of these elaborate neural systems and their interactions with the homeostatic regulator in the hypothalamus are poorly understood. These systems are directly and primarily involved in the interactions of the modern environment and lifestyle with the human body. They are no less physiological than metabolic regulatory mechanisms that have attracted most of the research during the past 15 years.

This review aims to provide a brief overview of the current concepts of neural control of food reward and the possible involvement of abnormal food reward processing in causing hyperphagia and obesity and potential maladaptive effects of palatable diets on reward processing. Two excellent recent reviews have discussed the relation of obesity to food reward from mainly the clinical and psychological perspective (108, 174). Here, we focus on neural correlates of reward, the interactions between reward and homeostatic functions, and the disturbance of this relationship in obesity (Fig. 2).

Glossary

Definitions were adopted from Berridge et al. (12):

Food Reward

A composite process that contains "liking" (hedonic impact), "wanting" (incentive motivation), and learning (associ-

Address for reprint requests and other correspondence: H.-R. Berthoud, Pennington Biomedical Research Center, Neurobiology of Nutrition Laboratory, 6400 Perkins Rd., Baton Rouge, LA 70808 (e-mail: berthohr@pbrc.edu).

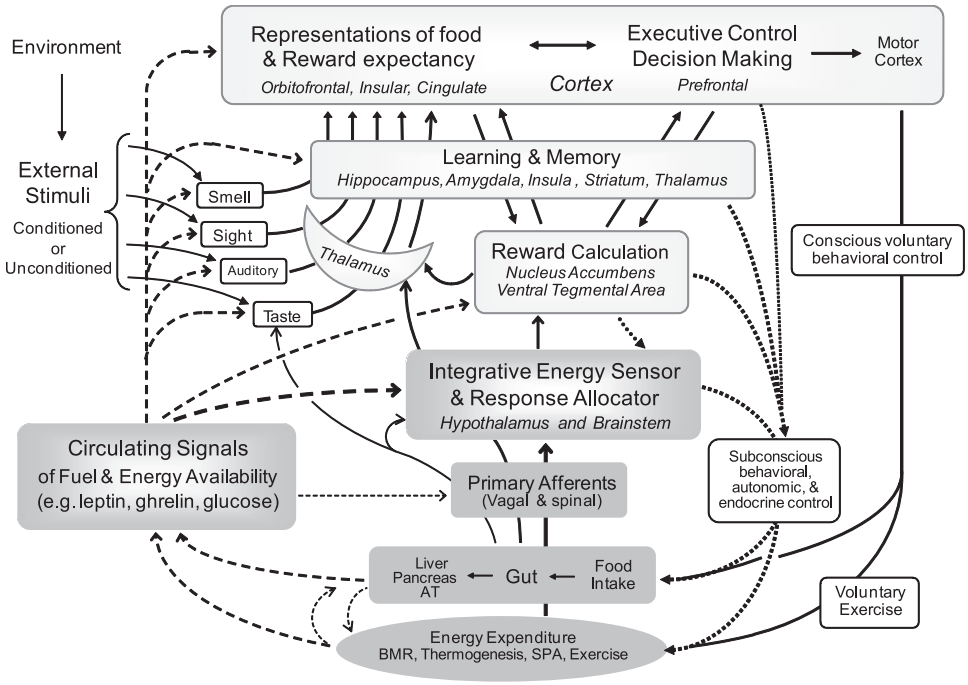

Fig. 1. Schematic flow diagram showing the relationship between the classical homeostatic regulator (dark gray boxes) and neural systems involved in reward, cognitive, and executive functions (light gray boxes). Note that humoral (broken lines with open arrows) and neural (full lines with open arrows) signals from peripheral organs handling energy assimilation and metabolism not only feed back to the hypothalamus and brainstem, but also to sensory and corticolimbic structures. Similarly, effector pathways can be accessed not only from hypothalamus and brainstem, but also from a number of corticolimbic structures (broken lines with closed arrows).

ations and predictions) as major components. Normally all occur together, but the three psychological components have separable brain systems that permit dissociation among them in some conditions.

"Liking" (with quotation marks)

An objective hedonic reaction detected in behavior or neural signals and generated chiefly by subcortical brain systems. A "liking" reaction to sweetness produces conscious pleasure by recruiting additional brain circuits, but a core "liking" reaction can sometimes occur without subjective pleasure.

Liking (without quotation marks)

The everyday sense of the word as a subjective conscious feeling of pleasurable niceness.

"Wanting" (with quotation marks)

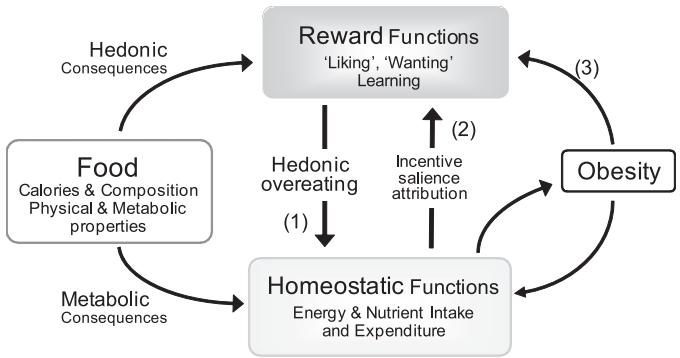

Fig. 2. Relationship between metabolic and hedonic controls of food intake and energy balance. The metabolic consequences of food are regulated by homeostatic functions and the hedonic consequences by reward functions. Hedonic and metabolic consequences are interdependent in that the hedonic value of food modulates caloric intake (*1*), and the metabolic status modulates hedonic processing (*2*). The obese state is associated with altered reward functions, but it is not clear whether these changes are the cause or consequence of obesity. Altered reward functions could cause obesity via increased intake of calories or fat (*1*), or alternatively, could result from consequences of the obese state (*3*), or could be a combination of both.

Incentive salience or motivation for reward typically triggered by reward-related cues. Attribution of incentive salience to the representations makes a cue and its reward more attractive, sought after, and likely to be consumed. Brain mesolimbic systems, especially those involving dopamine, are especially important to "wanting." Ordinarily "wanting" occurs together with other reward components of "liking" and learning and with subjective desires but can be dissociated both from other components and subjective desire under some conditions.

Wanting (without quotation marks)

A conscious, cognitive desire for a declarative goal in the ordinary sense of the word wanting. This cognitive form of wanting involves additional cortical brain mechanisms beyond the mesolimbic systems that mediate "wanting" as incentive salience.

Other definitions:

Palatable/Palatability

Foods that are acceptable or agreeable to the palate or taste. Synonyms include tasty or delectable. Generally, palatable foods are also energy-dense and include high-fat, high-sugar, or both, foods.

Sensory-Specific Satiety

The phenomenon wherein hungry animals satiate on one food and do not partake when offered the same food again; the same animals offered a second novel food consume another meal.

Metabolic Hunger

Hunger driven by metabolic need, mediated by endogenous signals of nutrient depletion.

Hedonic Hunger

Eating driven by other than metabolic need, such as external cues.

Hedonic Consequences of Food

The many pleasures of eating. Eating is typically experienced as pleasurable and rewarding, and it has been speculated

that the inherent pleasantness of eating has evolved to provide the necessary motivation to engage in this crucial behavior in adverse and hostile environments (94). Thus, food is a powerful natural reinforcer that out competes most other behaviors, particularly when an individual is metabolically hungry. Ingestive behavior is not limited to the act of eating, but consists of preparatory, consummatory, and postconsummatory phases (15). Hedonic evaluation and reward processing is carried out in each of these three phases of ingestive behavior and critically determines their outcome.

In the preparatory phase, before any oral contact is made with food, reward expectancy plays a pivotal role. This phase can be further divided into an initiation phase (switch of attention from another behavior) a procurement phase (planning, foraging), and an appetitive phase (seeing and smelling food). The initiation phase is the key process in which a choice, selection, or decision is made to pursue a particular goal-directed activity and not another one. The decision-making process responsible for switching attention is central to the modern field of neuroeconomics, and reward expectancy is perhaps the main factor determining the outcome of this process. Research suggests that to make this choice, the brain uses representations of reward-expectancy and effort/risk requirement from prior experiences to optimize cost/benefit (76, 111, 118, 139, 148). Thus, the decision to pursue this new goal largely depends on expecting but not actually consuming the reward. The time period between making a decision and actually being able to consume the reward is the procurement phase. This phase used to be quite long in our human ancestors and in today's free-living animals, as e.g., illustrated by the Canadian mountain goat descending from higher elevations to the river bed over a hundred miles to satisfy its salt appetite. Reward expectancy appears to be the main driver to keep focused during this journey. During the appetitive phase, immediate sensory attributes of the goal object such as seeing, smelling, and ultimately tasting the first bite of the food start to provide the first feedback to its predicted reward value and may acutely enhance its motivating power. This amplification of appetite is reflected by the generation of cephalic phase responses, anecdotally known by the French as l'appetit vient en mangeant (appetite grows with the first bites). The first bite is also the last chance to reject food if it does not fulfill expectations or is even toxic.

The consummatory phase (meal) starts when, based on the first bite, the initial reward expectancy is confirmed or surpassed. During eating, immediate, direct pleasure is derived from mainly gustatory and olfactory sensations, driving consumption throughout the meal until satiation signals dominate (166). The length of the consummatory phase is highly variable as it takes only a few minutes to devour a hamburger, but may take hours to savor a five-course meal. During such longer meals, ingested food increasingly engages postoral reward processes that interact with oral reward.

The postconsummatory phase starts at meal termination and lasts all the way to the next ingestive bout. This phase is probably the most complex and least understood phase of ingestive behavior in terms of reward processing, although the mechanisms of satiation and satiety have been exhaustively studied and a long list of satiety factors have been identified. As mentioned above, nutrient sensors in the gastrointestinal tract and elsewhere in the body appear to also contribute to the generation of food reward during and after a meal (153). The same taste receptors found in the oral cavity are also expressed in gut epithelial cells (144) and in the hypothalamus (131). But even when all taste processing is eliminated by genetic manipulation, mice still learn to prefer sugar over water, suggesting the generation of food reward by processes of glucose utilization (44). Rather than the acute pleasure of tasty food in the mouth, there is a general feeling of satisfaction that lingers on long after termination, and most likely contributes to the reinforcing power of a meal. Furthermore, in humans, meals are often embedded in enjoyable social interactions and a pleasant ambiance. Finally, knowledge that eating particular foods or reducing caloric intake will pay off by being healthier and living longer can generate yet another form of happiness or reward.

Thus, a variety of sensory stimuli and emotional states or feelings with vastly different temporal profiles make up the rewarding experience of eating, and the underlying neural functions are only beginning to be understood.

Neural mechanisms of food reward functions: liking and wanting. Just as there is no hunger center, there is no pleasure center in the brain. Given the complex involvement of pleasure and reward in ingestive (and other) motivated behaviors as outlined above, it is clear that multiple neural systems are involved. Neural systems activated by thinking about a favorite dish, savoring a candy in the mouth, or leaning back after a satiating meal, are likely very different, although they may contain common elements. To identify these differences and common elements is the ultimate goal of researchers in the field of ingestive behavior.

Perhaps the most easily accessible process is the acute pleasure generated by a candy in the mouth. Even in the fruit fly with its primitive nervous system, stimulation of gustatory neurons with sugar activated, while stimulation with a bitter substance inhibited, a pair of motor neurons in the subesophageal ganglion, leading to either vigorous ingestion or rejection (68), adding to the mounting evidence that taste evolved as a hardwired system telling the animal to either accept or reject certain foods. In mice with transgenic expression of the receptor for an ordinarily tasteless ligand in either sweet or bitter taste receptor cells, stimulation with the ligand produced either strong attraction or avoidance of sweet solutions, respectively (197). Most remarkably, quinine, a cognate bitter ligand, produced strong attraction in mice with expression of a bitter receptor in sweet-sensing taste receptor cells (114). These findings suggest that the most primitive form of liking and disliking may already be inherent to components of the peripheral gustatory pathways. As demonstrated in the decerebrate rat (70) and anencephalic baby (171), expression of the characteristic happy face when tasting sweets (11, 13) appears to be neurologically organized within the brainstem, suggesting that the forebrain is not necessary for expression of this most primitive form of core "liking" (13). In mammals, the caudal brainstem is the equivalent of the subesophageal ganglion, where direct sensory feedback from the tongue and the gut are integrated into basic motor patterns of ingestion (166, 179). Thus, this basic brainstem circuitry appears to be able to recognize the usefulness and perhaps pleasantness of a taste stimulus and initiate appropriate behavioral responses.

However, even if some of this primitive taste-guided reflexive behavior is organized within the brainstem, it is clear that

the brainstem circuits are normally not acting in isolation, but are intimately communicating with the forebrain. Even in *Drosophila*, the taste-specific receptor cells do not directly synapse on motor neurons responsible for the taste-guided behavioral output (68), leaving plenty of opportunities for modulatory influences from other areas of the nervous system. Clearly, for the full sensory impact of palatable food, and the subjective feeling of pleasure in humans, taste is integrated with other sensory modalities such as smell and mouth feel in forebrain areas including the amygdala, as well as primary and higher-order sensory cortical areas, including the insular and orbitofrontal cortex, to form sensory representations of particular foods (43, 45, 136, 141, 163, 164, 186). The exact neural pathways through which such sensory percepts or representations lead to the generation of subjective pleasure (Berridge's "liking", see *Glossary*) are not clear. Neuroimaging studies in humans suggest that pleasure, as measured by subjective ratings, is computed within portions of the orbitofrontal and perhaps insular cortex (13, 99).

In animals, only the subconscious components of pleasure (Berridge's core "liking") and aversion are experimentally accessible, and one of the few specific test paradigms is measurement of positive and negative orofacial expressions when tasting pleasurable (typically sweet) or aversive stimuli (11). Using this method, Berridge and colleagues (12, 122) have demonstrated narrowly circumscribed, μ-opioid receptor-mediated pleasure ("liking") hotspots in the nucleus accumbens shell and ventral pallidum. We have recently demonstrated that nucleus accumbens injection of a μ-opioid receptor antagonist transiently suppressed such sucrose-evoked positive hedonic orofacial reactions (158). Together the findings suggest that endogenous μ-opioid signaling in the nucleus accumbens (ventral striatum) is critically involved in the expression of "liking." Because the measured behavioral output is organized within the brainstem, the ventral striatal "liking" hotspot must somehow communicate with this basic reflex circuitry, but the pathways of communication are unclear.

One of the key questions is how motivation to obtain a reward is translated into action (113). In most instances, motivation comes to fruition by going for something that has generated pleasure in the past, or in other words by wanting what is liked. Dopamine signaling within the mesolimbic dopamine projection system appears to be a crucial component of this process. Phasic activity of dopamine neuron projections from the ventral tegmental area to the nucleus accumbens in the ventral striatum are specifically involved in the decision-making process during the preparatory (appetitive) phase of ingestive behavior (26, 148). In addition, when palatable foods such as sucrose are actually consumed, a sustained and sweetness-dependent increase occurs in nucleus accumbens dopamine levels and turnover (75, 80, 165). Dopamine signaling in the nucleus accumbens thus appears to play a role in both the preparatory and consummatory phases of an ingestive bout. The nucleus accumbens shell is thereby part of a neural loop including the lateral hypothalamus and the ventral tegmental area, with orexin neurons playing a key role (7, 22, 77, 98, 115, 125, 175, 199). This loop is likely important for the attribution of incentive salience to goal objects by metabolic state signals available to the lateral hypothalamus, as discussed below.

In summary, although there have been excellent recent attempts to separate its components, the functional concept and neural circuitry underlying food reward is still poorly defined. Specifically, it is not well understood how reward, generated during anticipation, consummation, and satiation, are computed and integrated. Future research with modern neuroimaging techniques in humans and invasive neurochemical analyses in animals will be necessary for a more complete understanding. Perhaps the most important processing step in the translation of such sensory representations into actions is the attribution of what Berridge calls "incentive salience." This mechanism allows a starving animal to know it needs calories or a salt-depleted organism to know it needs salt. The modulation of hedonic processes by the metabolic state is discussed below.

Metabolic State Modulates Hedonic Processing

The metabolic consequences of ingested food are defined here in terms of their input of energy and their effects on body composition, particularly increased fat accretion as in obesity. Together with the control of energy expenditure, these functions are known as homeostatic regulation of body weight and adiposity (Fig. 1). It has long been known that metabolic hunger increases motivation to find food and to eat, but the neural mechanisms involved were obscure. Given that the hypothalamus was recognized as the epicenter of homeostatic regulation, it was assumed that the metabolic hunger signal originates in this brain area and propagates through neural projections to other areas important for the organization of goal-directed behavior. Thus, when leptin was discovered, researchers were initially content to limit their search for leptin receptors to the hypothalamus, and the initial localization to the arcuate nucleus further propagated the hypothalamocentric view (29, 150). However, during the last few years it became increasingly clear that leptin and the plethora of other metabolic signals not only act on the hypothalamus, but on a large number of brain systems.

Modulation via the hypothalamus. Within the hypothalamus, the arcuate nucleus with its neuropeptide Y and proopiomelanocortin neurons had been originally thought to play an exclusive role in integrating metabolic signals. But clearly, leptin receptors are located in other hypothalamic areas such as the ventromedial, dorsomedial, and premammillary nuclei, as well as the lateral and perifornical areas where they likely contribute to leptin's effects on food intake and energy expenditure (101, 102). It has long been known that electrical stimulation of the lateral hypothalamus elicits food intake and that rats learn quickly to self-administer electrical stimulation (83, 183). Metabolic signals modulate the stimulation threshold for lateral hypothalamic elicited self-stimulation and feeding (16, 17, 20, 64, 81–83, 89). Recent investigations show that lateral hypothalamic neurons expressing orexin (77, 199) and other transmitters such as neurotensin (101, 107) provide modulatory input to midbrain dopamine neurons well known to be crucial players in translating motivation into action (10, 14, 22, 42, 77, 91, 148, 194, 196). Orexin neurons can integrate various metabolic state signals such as leptin, insulin, and glucose (2, 25, 51, 107, 160). In addition to midbrain dopamine neurons, orexin neurons project widely within both forebrain and hindbrain. In particular, a hypothalamic-thalamic-striatal loop involving orexin projections to the paraventricular nucleus of the thalamus and cholinergic striatal interneurons (93), and orexin projections to oromotor and autonomic motor areas in the

caudal brainstem (6). All of these strategic projections put lateral hypothalamic orexin neurons in an ideal position to link internal needs with environmental possibilities to make optimal adaptive choices.

Modulation of "wanting" through the mesolimbic dopamine system. Considerable evidence has recently accumulated for a direct modulation of midbrain dopamine neurons by metabolic state signals. After the initial demonstration that leptin and insulin injections directly into this brain area suppressed expression of food-conditioned place preference (61), other studies demonstrated that such leptin injections decreased dopamine neuron activity and acutely suppressed food intake, while adenoviral knockdown of leptin receptors specifically in the ventral tegmental area (VTA) resulted in increased sucrose preference and sustained palatable food intake (84). In contrast, ghrelin action directly within the VTA appears to activate dopamine neurons, increase accumbens dopamine turnover, and increase food intake (1, 88, 116). Together, these findings suggest that part of the orexigenic drive of ghrelin and the anorexigenic drive of leptin is achieved by direct modulation of reward-seeking functions mediated by midbrain dopamine neurons. However, this modulation may be more complex, as leptin-deficient mice (absence of leptin-receptor signaling) exhibit suppressed rather than increased dopamine neuron activity [as expected from the viral knockdown experiments in rats (84)], and leptin-replacement therapy restored normal dopamine neuron activity as well as amphetamine-induced locomotor sensitization (63). Also, in normal rats, leptin promotes tyrosine hydroxylase activity and amphetamine-mediated dopamine efflux in the nucleus accumbens (119, 124). This opens up the interesting possibility that a suppressed mesolimbic dopamine signaling system (rather than an overactive one) is associated with development of compensatory hyperphagia and obesity, as proposed by the reward-deficiency hypothesis discussed in the next main section. Under this scenario, leptin would be expected to increase dopamine-signaling efficiency rather than suppress it.

Modulation of "liking" through sensory processing, cortical representation, and cognitive controls. As elaborated above, food-related visual, olfactory, gustatory, and other information converges in polymodal association and related areas such as the orbitofrontal cortex, insula, and amygdala, where it is thought to form representations of experience with food to guide current and future behavior. Recent studies suggest that the sensitivity of these sensory channels and activity within the orbitofrontal cortex, amygdala, and insula are modulated by metabolic state signals.

In rodents, absence of leptin has been shown to increase and addition of leptin to dampen peripheral taste and olfactory sensitivity (66, 90, 157). Leptin may also modulate sensory processing at higher gustatory and olfactory processing steps, as indicated by the presence of leptin receptors and leptin-induced Fos expression in the nucleus of the solitary tract, parabrachial nucleus, olfactory bulb, and insular and piriform cortices of rodents (53, 74, 86, 112, 159).

In the orbitofrontal cortex and amygdala of monkeys, individual neurons responsive to the taste of specific nutrients such as glucose, amino acids, and fat were modulated by hunger in a sensory-specific manner (137, 138, 140, 141). Similarly, subjective pleasantness in humans was coded by neural activity in the medial orbitofrontal cortex as measured by functional MRI (fMRI) and was subject to sensory-specific satiety, a form of reinforcer devaluation (45, 100, 117, 135).

Also by fMRI measurement, it was shown that taste-induced changes in neuronal activation occurred within several areas of the human insular and orbitofrontal cortex and preferentially in the right hemisphere (164). Comparing the fasted vs. fed state, food deprivation increased activation of visual (occipitotemporal cortex) and gustatory (insular cortex) sensory processing areas by the sight and taste of food (181). In another study, pictures of food that elicited strong activation of visual and premotor cortex, hippocampus, and hypothalamus under eucaloric conditions, elicited much weaker activation after 2 days of overfeeding (30). In a recent study exploring the functional neurological consequences of dieting in obese humans, it was found that after a diet-induced 10% body weight loss, neural changes induced by visual food cues were significantly enhanced in several brain areas dealing with higher-order sensory perception and processing of working memory, including an area in the middle temporal gyrus involved in higher-order visual processing (142). Both of these weight loss-induced differences were reversed after leptin treatment, suggesting that low leptin sensitizes brain areas responding to food cues. Neural activation 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 (57). In the leptin-deficient state, nucleus accumbens activation was positively correlated with ratings of liking for the food shown in images in both the fasted and fed state. Even foods considered bland under normal conditions (with leptin in the satiated state) were liked very much in the absence of leptin signaling. After leptin treatment in these leptin-deficient patients, and in normal subjects, nucleus accumbens activation was only correlated with ratings of liking in the fasted state (57).

Furthermore, neural activity in brain areas thought to be involved in cognitive processing of representations of food such as the amygdala and hippocampal complex is modulated by leptin (78, 79, 105) and ghrelin (27, 50, 92, 109, 147, 189). Thus, it is quite clear that processes of subconscious hedonic evaluation and subjective experience of pleasantness in animals and humans are modulated by the internal state.

In summary, metabolic state signals impinge on almost every neural process involved in procuring, consuming, and learning about food. It is thus unlikely that the mechanisms attributing incentive salience to appetitive stimuli are exclusively originating from nutrient-sensing areas in the mediobasal hypothalamus. Rather, this life-sustaining process is organized in a redundant and distributed fashion.

Food Reward and Obesity

As schematically depicted in Fig. 2, several potential interactions exist between food reward and obesity. The discussion here will focus on three fundamental mechanisms: *1*) genetic and other preexisting differences in reward functions potentially causing obesity; *2*) intake of palatable food as an escalating, addictive process leading to obesity; and *3*) acceleration of obesity through changes in reward functions induced by secondary effects of the obese state. These mechanisms are not mutually exclusive, and it is highly likely that a combination of all three is operative in most individuals. It is also important to

realize that hyperphagia is not always necessary for obesity to develop, as the macronutrient composition of food can independently favor fat deposition.

Do genetic and other preexisting differences in reward functions cause obesity? One fundamental premise here is that unlimited access to palatable food leads to hedonic overeating and eventually obesity, called the gluttony hypothesis for simplicity. This hypothesis is supported by numerous studies in animals demonstrating increased intake of palatable foods and development of obesity, so called diet-induced obesity (143, 151, 152, 154, 167, 178, 180, 193, 195). There are also plenty of human studies showing acute effects of manipulating palatability, variability, and availability of food (191, 192), although few controlled studies show long-term effects on energy balance (120, 134).

In its purest form, the gluttony hypothesis does not require reward functions to be abnormal; it only requires the environmental conditions to be abnormal (increased access to palatable foods and exposure to cues). Although environmental pressure undoubtedly pushes the general population to higher food intake and body weight, this simple explanation does not account for the fact that not all subjects exposed to the same toxic environment gain weight. This suggests that preexisting differences make some individuals more vulnerable to the increased availability of palatable food and food cues, and the crucial question is what these differences might be. Here we argue that differences in reward functions are responsible, but it is equally possible that differences in the way the homeostatic system handles hedonic overeating are important. Under this scenario, an individual would show all signs of acute hedonic overeating, but the homeostatic regulator (or other mechanisms causing negative energy balance) would be able to counteract this effect over the long term.

Preexisting differences could be determined by genetic and epigenetic alterations, and by early life experience through developmental programming. Among the 20 or so major genes (clear evidence from at least two independent studies) linked to the development of obesity (129), none are directly implicated in known mechanisms of reward functions. However, because the combined effect of these genes only accounts for less than ~5% of human obesity, it is very likely that many important genes have not yet been discovered, some of which could operate within the reward system.

There is a considerable body of literature demonstrating differences in reward functions between lean and obese animals and humans (40, 162, 173, 174). Such differences could exist before the development of obesity or could be secondary to the obese state, but few studies have attempted to dissociate these two mechanisms. It is also important to note that preexisting differences in reward functions do not automatically result in obesity later in life.

Comparing lean and obese subjects carrying different alleles of either the dopamine D2-receptor or μ-opioid receptor genes does reveal differences in behavioral and neural responses to palatable food (39, 40, 60, 172). In selectively bred lines of obesity-prone and obesity-resistant rats, several differences in mesolimbic dopamine signaling have been reported (41, 65), but most of these studies used adult, already obese animals. In only one preliminary study was a difference seen at an early age (65), so it is not clear whether differences in reward functions are preexisting and genetically determined or acquired by exposure to palatable food stimuli and/or secondary to the obese state. Because obesity-prone rats develop some degree of obesity even on regular chow diet, it is also not clear to what extent the genetic difference depends on availability of palatable diet vs. chow, to be phenotypically expressed (susceptibility genes). Mesolimbic dopamine signaling is also severely suppressed in leptin-deficient *ob/ob* mice and rescued by systemic leptin replacement (63). However, in genetically leptin-deficient humans, neural activity in the nucleus accumbens elicited by viewing pictures of palatable foods was exaggerated in the absence of leptin and abolished after leptin administration (57). Furthermore, PET neuroimaging showed reduced dopamine D2-receptor availability mostly in the dorsal and lateral, but not ventral, striatum (187). On the basis of this last observation, the reward-deficiency hypothesis was coined, suggesting that increased food intake is an attempt to generate more reward in compensation for reduced mesolimbic dopamine signaling (19, 128, 187). Clearly, evidence not confounded by differences in subjects and methodology is needed for clarity in understanding of how mesolimbic dopamine signaling is involved in hyperphagia of palatable food and the development of obesity.

Besides classical genetic, epigenetic and nongenetic mechanisms (23, 34, 36, 37, 62, 67, 126, 155, 176, 184) could also be potentially responsible for differences in neural reward circuitry and reward behaviors at a young age, predisposing to hyperphagia and obesity later in life. Such effects are best demonstrated in genetically identical C57/BL6J inbred mice or identical twins. In one such study, only about half of male C57/BL6J mice became obese on a palatable high-fat diet (55), but reward functions were not assessed.

In summary, differences in mesolimbic dopamine signaling are most strongly implicated in altered food anticipatory and consummatory behaviors and obesity. However, it is still unclear to what extent preexisting differences and/or secondary effects determine these behavioral alterations and cause obesity. Only longitudinal studies in genetically defined populations will provide more conclusive answers.

Is repeated exposure to addictive foods changing reward mechanisms and leading to accelerated development of obesity? There is heated discussion about similarities between food and drug addiction (32, 38, 49, 56, 69, 94, 104, 123, 133, 187, 188). While the field of drug addiction has a long tradition (e.g., Refs. 96, 132), the concept of food addiction is still not generally accepted, and its behavioral and neurological mechanisms remain obscure. It is well-known that repeated exposure to drugs of abuse causes neuroadaptive changes leading to elevations in reward thresholds (decreased reward) that drive accelerated drug intake (4, 87, 96, 97, 110, 145). The question here is whether repeated exposure to palatable food can lead to similar neuroadaptive changes in the food-reward system and behavioral dependence (craving for palatable foods and withdrawal symptoms) and whether this is independent from obesity that typically results after prolonged exposure to palatable foods. The limited information available suggests that repeated sucrose access can upregulate dopamine release (5) and dopamine transporter (9), and change dopamine D1 and D2 receptor availability (5, 8) in the nucleus accumbens. These changes may be responsible for the observed escalation of sucrose bingeing, cross-sensitization to amphetamine-induced locomotor activity, withdrawal symptoms, such as increased anxiety

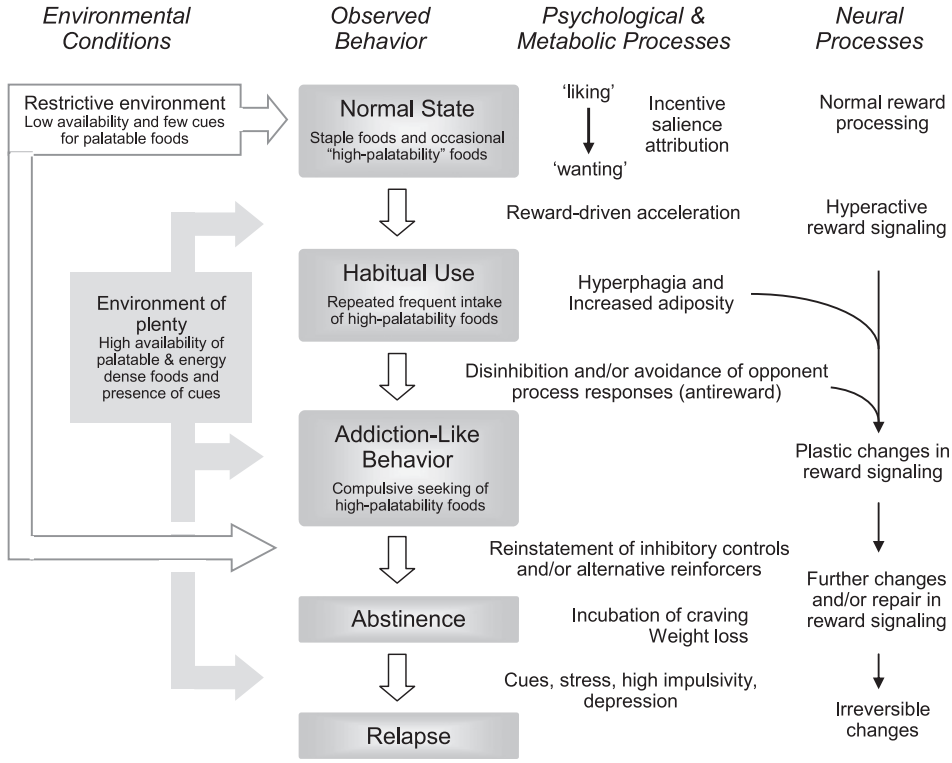

Fig. 3. Conceptual representation of mechanisms in palatable food-induced hyperphagia. An environment of plenty favors habitual intake of palatable foods that can accelerate to an addiction-like state when normal reward processing is corrupted by hyperactivity and/or neurotoxic effects of obesity. Reinstatement of inhibitory controls and/or a change in environment can result in abstinence.

and depression (5), as well as reduced reinforcing efficacy of normal foods (33). For nonsweet palatable foods (typically high-fat foods), there is less convincing evidence for development of dependence (21, 31), although intermittent access to corn oil can stimulate dopamine release in the nucleus accumbens (106).

In Wistar rats, exposure to a palatable cafeteria diet led to sustained hyperphagia over 40 days and lateral hypothalamic electrical self-stimulation threshold increased in parallel to body weight gain (89). A similar insensitivity of the reward system was previously seen in addicted rats, self-administering intravenous cocaine or heroin (4, 110). Furthermore, dopamine D2-receptor expression in the dorsal striatum was significantly reduced in parallel to worsening of the reward threshold (89), to levels found in cocaine-addicted rats (35). Interestingly, after 14 days of abstinence from the palatable diet, reward threshold did not normalize even though the rats were hypophagic and lost ~10% body weight (89). This is in contrast to the relatively rapid (~48 h) normalization in reward thresholds in rats abstaining from cocaine self-administration (110) and may indicate the presence of irreversible changes caused by the high-fat content of the diet (see next section). Given the observation that cocaine addicts and obese human subjects exhibit low D2R availability in the dorsal striatum (190), these findings suggest that dopamine plasticity due to repeated consumption of palatable food is somewhat similar to that due to repeated consumption of drugs of abuse.

As with drug (71, 96, 156) and alcohol (18, 185) addiction, abstinence from sucrose can cause craving and withdrawal symptoms (5), eventually leading to relapse behavior (72, 73). It is thought that abstinence incubates further neural and molecular changes (28, 185), facilitating cue-evoked retrieval of automated behavioral programs. Therefore, relapse behavior has come under intense investigation as it is key for interrupting the addictive cycle and prevention of further spiraling dependence (156). Little is known how this incubation affects "liking" and "wanting" of palatable food and how it interacts with obesity, and the schematic diagram in Fig. 3 is an attempt to outline the major pathways and processes.

In summary, early observations in rodents suggest that some palatable foods such as sucrose have addictive potential in certain experimental animal models, as they recapitulate at least some key criteria established for drugs and alcohol. However, much further research is necessary to obtain a clearer picture of the abuse potential of certain foods and the neural pathways involved.

Is the obese state changing reward mechanisms and accelerating the process? Obesity is associated with dysregulated signaling systems, such as leptin and insulin resistance, as well

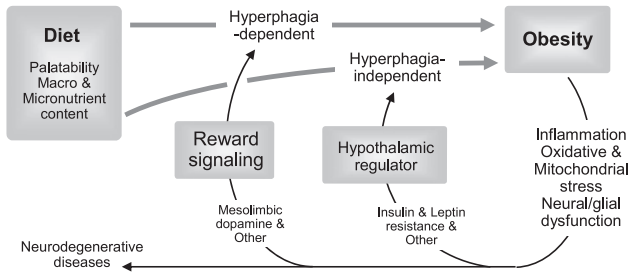

Fig. 4. Secondary effects of obesity on reward circuitry and hypothalamic energy balance regulation. Palatable and high-fat diets can lead to obesity with or without hyperphagia. Increased inflammatory, mitochondrial, and oxidative stress signaling within the brain leads to neural/microglial alterations impinging on the hypothalamus and corticolimbic systems involved in reward functions, accelerating the development of obesity.

as increased signaling through proinflammatory cytokines and pathways activated by oxidative and endoplasmatic reticulum stress (3). It is becoming clear that the obesity-induced toxic internal environment does not spare the brain (24, 46, 48, 52, 59, 95, 121, 127, 177, 182, 198). Obesity-induced brain insulin resistance is believed to have a direct effect on development of Alzheimer's disease now also called type 3 diabetes (46, 47) as well as other neurodegenerative diseases (161).

A number of recent studies directed attention to the hypothalamus, where high-fat diets disturb the delicate relationship between glial cells and neurons through increased endoplasmic reticulum and oxidative stress, leading to stress-response pathways with generally cytotoxic effects (48, 121, 177, 198). The end effects of these changes are central insulin and leptin resistance and impaired hypothalamic regulation of energy balance, further favoring the development of obesity and in turn, neurodegeneration. However, these toxic effects do not stop at the level of the hypothalamus, but can also affect brain areas involved in reward processing. The obese, leptin-deficient mouse is much more sensitive to chemically-induced neurodegeneration such as metamphetamine-induced dopamine nerve terminal degeneration as indicated by reduced striatal dopamine levels (170). Obesity and hypertriglyceridemia produce cognitive impairment in mice, including reduced lever pressing for food reward (59), and epidemiological studies show an association of body mass index and risk of Parkinson disease and cognitive decline (85). Obesity-prone rats allowed to become obese on regular chow, or fed amounts of high-fat diet so as not to gain extra body weight, exhibited significantly reduced operant responding (progressive ratio break point) for sucrose, amphetamine-induced conditioned place preference, and dopamine turnover in the nucleus accumbens (41). These results suggest that both obesity per se and high-fat diet can cause alterations in mesolimbic dopamine signaling and reward behaviors. Possible pathways and mechanisms by which dietary manipulations and obesity could affect neural reward circuitry are shown in Fig. 4.

In summary, it seems clear that the obesity-induced internal toxic environment does not stop at the level of the brain, and within the brain does not stop at the reward circuitry. Just like brain areas involved in homeostatic energy balance regulation, such as the hypothalamus, and in cognitive control, such as the hippocampus and neocortex, reward circuitry in corticolimbic and other areas is likely to be affected by obesity-induced changes in peripheral signals to the brain and local brain signaling through inflammatory, oxidative, and mitochondrial stress pathways.

Conclusions and Perspectives

Obesity clearly is a multifactorial disease with a number of potential causes, but the involvement of recent environmental changes including overabundance of palatable food and little opportunity to work off the extra energy seems undeniable. Given these external conditions together with the strong inherent bias of the homeostatic regulatory system to defend against energy depletion more strongly than energy surplus, weight is easily gained but not so easily lost. This review examines the evidence for individual differences in brain reward mechanisms as being responsible for either becoming obese or staying lean in the modern environment. Although there is considerable indirect and correlative evidence for involvement of the reward system in causing obesity in both animals and humans, there is no smoking gun for a single specific neural pathway or molecule. This is most likely because the reward system is complex and cannot be easily manipulated with drugs or genetic deletions. The most convincing evidence exists for a role of the mesolimbic dopamine pathway in the "wanting" aspect of ingestive behavior, but it is not yet clear whether over- or under-activity of dopamine signaling is at the origin of hyperphagia. Furthermore, it is not yet clear whether mesolimbic dopamine projections to selective targets in the basal ganglia, cortex, or hypothalamus are specifically involved. However, the final decision to ingest a food item, whether it is the result of conscious reasoning or subconscious emotional processing, is perhaps the most important neural process. Besides instant gratification, it takes into account the achievement of a deeper happiness that comes from living a healthy, harmonious, and successful life. For example, some individuals derive pleasure and happiness from physical activity and its long-term effects. Yet, we do not understand how the brain computes this longer-term reward and how it is integrated with the more instant pleasures.

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No conflicts of interest, financial or otherwise, are declared by the author(s).

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