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Neural Systems Controlling the Drive to Eat: Mind Versus Metabolism

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With the bleak outlook that 75% of Americans will be overweight or obese in 10 years, it is essential to find efficient help very soon. Knowledge of the powerful and complex neural systems conferring the basic drive to eat is a prerequisite for designing efficient therapies. Recent studies suggest that the cross talk between brain areas involved in cognitive, emotional, and metabolic-regulatory functions may explain why energy homeostasis breaks down for many predisposed individuals in our modern environment.

The obesity epidemic continues unabated (47, 48, 55, 84, 87). It causes secondary health risks such as Type 2 diabetes, cardiovascular disease, sleep apnea, and depression that significantly reduce the quality of life and burden the public health system. With little or no effective treatments available, it is important to come to a better understanding of the controls of appetite and body weight and the major factors contributing to their breakdown in obesity. Genetic predisposition and physiology are important determinants of proper functioning of these control systems, but clearly the changing environment and lifestyle are the primary engines of the obesity epidemic.

Essential Physiological Functions Require Powerful and Foolproof Control Systems

Given its vital importance, procurement of sufficient energy and essential nutrients is defended by a complex system consisting of redundant pathways to make it fail-safe. The major components of this system are accurate sensors of the internal milieu and the external world, flexible and adaptive integrators that make sense out of all this diverse input, and powerful effectors that act on both the input and the output arm of energy balance (FIGURE 1). Research efforts in the post-leptin discovery era have mainly focused on the "metabolic brain," identifying some of the crucial neural circuits in hypothalamus and hindbrain. However, to understand how metabolic need is translated into strong behavioral actions that successfully compete with other motivated behavior, the role of the "cognitive and emotional brain" cannot be neglected. Investigating how the two domains interact with each other might be particularly fruitful.

Ingested Nutrients Generate a Host of Signals Used by the Brain and Peripheral Organs

To make decisions, the brain keeps track of internal nutrient availability, a process often referred to as nutrient sensing. Although nutrients circulating in the blood satisfy immediate needs and are sensed continuously, information from stored nutrients and nutrients ready to be absorbed from the gut are in many ways more important, because they safeguard supply over longer time periods and decrease vulnerability to external factors.

Nutrients in the gut signal future availability and satiation

Both the absence and presence of nutrients in the gastrointestinal tract generates powerful signals informing the brain and other peripheral organs (FIGURE 2). Ghrelin secreted from the mucosa of the empty stomach is the only known hormone to stimulate ingestive behavior in a feed-forward fashion (22, 23). Its plasma levels peak just before meals are requested and decline rapidly after nutrients enter the duodenum. Ghrelin may be the explanation for "hunger pangs" thought to originate from the empty stomach mucosa rubbing against each other. Ghrelin not only affects the homeostatic energy regulator in the hypothalamus but also has widespread effects on brain areas important for efficient foraging behavior (see below).

All other known gut signals essentially produce satiation of hunger, with little evidence that their absence reciprocally stimulates hunger. In the stomach, such signals include mechanical distension of vagal stretch and tension receptors and locally produced leptin acting on vagal afferents (4, 65, 86, 91). The bowel generates a number of nutrient-related signals with some degree of macronutrient-specific encoding as an emerging principle (FIGURE 2). Although fat and protein appear to signal primarily through the release of CCK and perhaps PYY(3-36) (34, 43, 68, 76), glucose signaling may involve the sweet-specific G-protein-coupled taste receptor-1 heterodimers T1R2+3, the sodium-glucose transporter, and ultimately the release of 5-HT and GLP-1 from enteroendocrine cells (31, 38, 49, 50). It will be interesting to see whether "taste receptors" are more generally used by the gut to drive nutrient-specific patterns of hormone release, thus encoding the macronutrient content of the gut. It

will be equally important to fully characterize other factors modulating hormone release from enteroendocrine cells, such as neural inputs from the enteric and autonomic nervous systems, paracrine inputs from neighboring enterocytes, and humoral inputs from the circulation. Perhaps, together with gastric volume sensors, intestinal nutrient sensors are able to quantitatively meter the gut content of each macronutrient available for absorption during the few hours after consumption.

Circulating nutrients signal immediate availability

Not only the brain, but also the pancreas, is interested in information regarding about-to-be-absorbed nutrients, since it secretes hormones important for efficient partitioning and stabilization of plasma levels of nutrients. This role of gut hormones on the endocrine pancreas was coined the incretin effect (FIGURE 2).

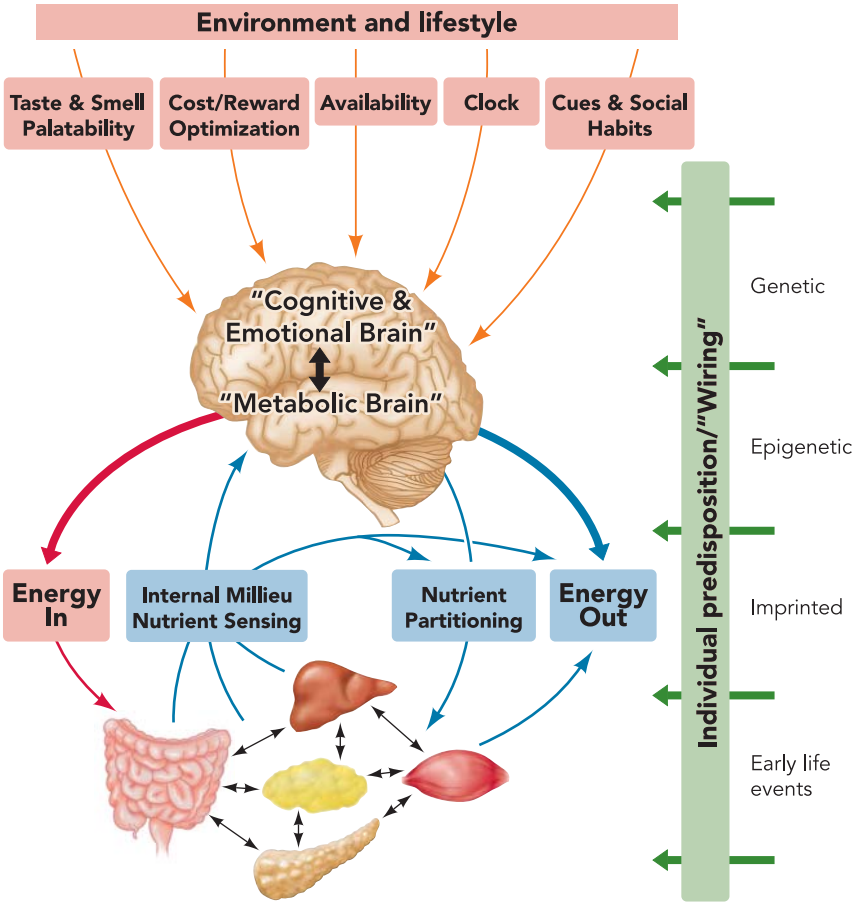

FIGURE 1. **Schematic diagram showing the major factors determining neural control of appetite and regulation of energy balance**
The brain monitors the internal milieu through a number of hormonal- and neural nutrient-sensing mechanisms and is under constant influence of the environment and lifestyle through the senses and mainly the cognitive and emotional brain. The two streams of information are integrated to generate adaptive behavioral (food intake) and autonomic/endocrine responses determining nutrient partitioning, energy expenditure, and overall energy balance. Any of the peripheral and central signaling steps are subject to individual predisposition through either genetic, epigenetic, or non-genetic early life imprinting mechanisms.

Together with circulating metabolites, incretins determine pancreatic secretion of a number of hormones that, in addition to their many peripheral actions, powerfully affect the brain. Given the exquisite glucose-sensitivity of the endocrine pancreatic hormone insulin and the co-secreted amylin, these two hormones provide important information regarding availability of the preferred brain fuel, glucose.

Although most of these signals act directly in the brain, some act on vagal sensory neurons innervating the portal vein and liver (12, 14, 15, 60). Particularly, a vagal sensor in the wall of the portal vein sensitive to circulating glucose and GLP-1 has gained attention since it may mediate the satiating effects of intestinal gluconeogenesis and GLP-1 (54) (FIGURE 2).

Stored nutrients signal long-term availability

White adipose tissue, far from being a passive fat storage organ, secretes a plethora of hormones and cytokines, some of which powerfully affect appetite and energy balance (80). Leptin is the most infamous hormone in energy balance regulation but has not turned out to be the magic bullet for the treatment of obesity. Although average plasma levels of leptin are positively correlated with total adiposity, fasting can rapidly suppress and re-feeding can rapidly augment leptin release, suggesting that plasma levels are rather tracking the acute nutritional state than signaling adiposity. The respective roles of the sympathetic nervous system and circulating nutrients and hormones in leptin secretion are still not completely understood.

Key Neurons in the Hypothalamus Integrate Metabolic Signals and Engage Specific Effector Pathways

Sensors and receptors for nutrition-relevant molecules are located in all major brain areas (FIGURE 2). Presence of receptors for a particular hormone typically leads to the site of its action. This is generally true for the brain too, except that some peptide hormones are also produced within the brain, making it difficult to distinguish the two sources of ligand and their specific sites of action. This is exemplified by GLP-1, which is produced not only in the lower gut but also in a population of neurons in the medulla with projections to the hypothalamus and receptors distributed in both of these brain areas.

Most molecules relevant for energy balance use specific transport systems to get across the blood-brain barrier, but there are several holes in this barrier, most prominently in the median eminence of the hypothalamus and the area postrema in the medulla oblongata (6, 7). Fully understanding the capacity and modulatory factors of these transporters may provide important tools for manipulating brain levels of relevant molecules.

NPY/AGRP and POMC/CART neurons: orchestrating survival and handling abundance

The neurocircuitry involved in energy balance regulation has been discussed in several in-depth reviews (12a, 33) and is, therefore, only briefly discussed here. Two populations of neurons, one expressing the powerfully orexigenic peptides NPY and AGRP and the other expressing the anorexigenic peptides POMC and CART, located in the arcuate nucleus of the hypothalamus are the primary integrators of various nutritional information (FIGURE 3). Both populations are directly and differentially sensitive not just to circulating leptin, but also to other hormones including insulin, ghrelin, and PYY(3-36), as well as to circulating metabolites including glucose, fatty acids, and amino acids (2, 20, 62).

Since progress has been made in defining the intracellular signaling pathways mediating the effects of these various hormonal, transmitter, and metabolite signals, it becomes apparent that the richness of these intracellular signaling pathways and their coupling to changes in neuronal excitability, peptide expression, and synaptic connectivity may provide the major substrate for integrative processes (FIGURE 3). Leptin engages a number of intracellular pathways, including those associated with cAMP, MAPK, Stat3, and PI3K (21, 56, 58, 61, 67, 73, 74, 77, 92).

AMPK, an evolutionarily conserved serine-threonine kinase activated by a high AMP-to-ATP ratio, indicating cellular energy depletion (90), stimulates food intake (53) and appears to be important for glucose sensing of POMC and AGRP neurons but not for the effects of leptin (18).

Mammalian target of rapamycin (mTOR) is another energy sensor that has assumed a specific functional role in hypothalamic regulation of energy balance. It is essential for the ability of amino acids to suppress food intake and regulate neuropeptide expression, and it may contribute to leptin and insulin action (20, 57). Since it also interacts with AMPK(51), mTOR may represent a potential site of convergence for both hormonal and nutrient sensing.

NPY/AgRP and POMC neurons interact on several levels. One is inhibition of POMC neurons via local axon collaterals from NPY neurons (21, 71). Since NPY neurons can also produce GABA, if activated, they inhibit POMC neurons through both NPY1 and GABAA receptors. In the absence of reciprocal inhibition of NPY neurons by POMC neurons, this

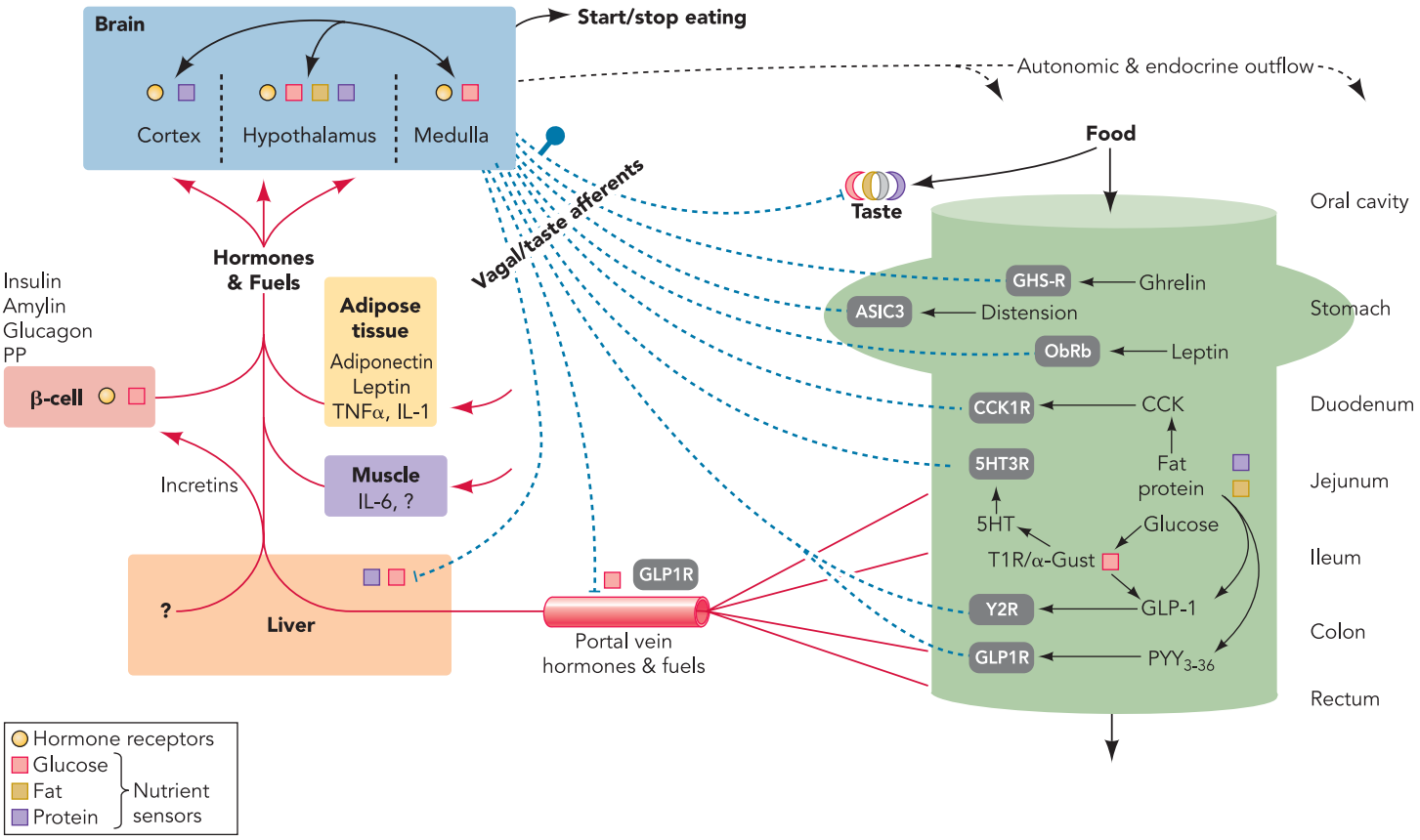

FIGURE 2. **Nutrient sensing by the brain**
Simplified schematic diagram showing the major pre- and postabsorptive transduction sites and mechanisms for the detection of ingested food and its macronutrient components. Nutrient information is sent to the brain through vagal and taste afferents (heavy broken lines) or through the blood circulation (solid lines). Specific receptors expressed by vagal afferent neurons are shown in rectangular boxes. Specific sensor mechanisms demonstrated for glucose, amino acids/proteins, and lipids/fatty acids are shown by gray, striped, and white squares, respectively.

arrangement may be interpreted as a fail-safe system to protect eating as the default mode of action. A second level of interaction occurs at downstream target neurons, since NPY/AgRP and POMC projections frequently converge on common downstream sites both within and outside the hypothalamus.

Autonomic, endocrine, and behavioral effector pathways

The major projection sites are second-order neuron populations in the lateral/perifornical hypothalamic area (LHA) and the paraventricular nucleus of the hypothalamus (PVH). These two brain regions are classically associated with the regulation of food intake and autonomic output, and each contains a variety of neuropeptide-expressing neurons associated with energy balance control. The prevailing model suggests that input from NPY/AgRP neurons is opposed by input from POMC neurons; this "metabolic" information is integrated with input from additional brain areas, and these downstream neurons in turn project widely to third and higher order neurons located in many areas of the brain and spinal cord (11).

Neurons within the LHA receiving direct input from the arcuate nucleus contain several food regulatory neuropeptides including orexin/hypocretin (HCRT), melanin-concentrating hormone (MCH), cocaine and amphetamine-regulated transcript (CART), neurotensin (NT), and histamine (FIGURE 3). Specific populations of LHA neurons also express leptin receptors, and some are sensitive to glucose. In addition to this metabolic information, the LHA also receives

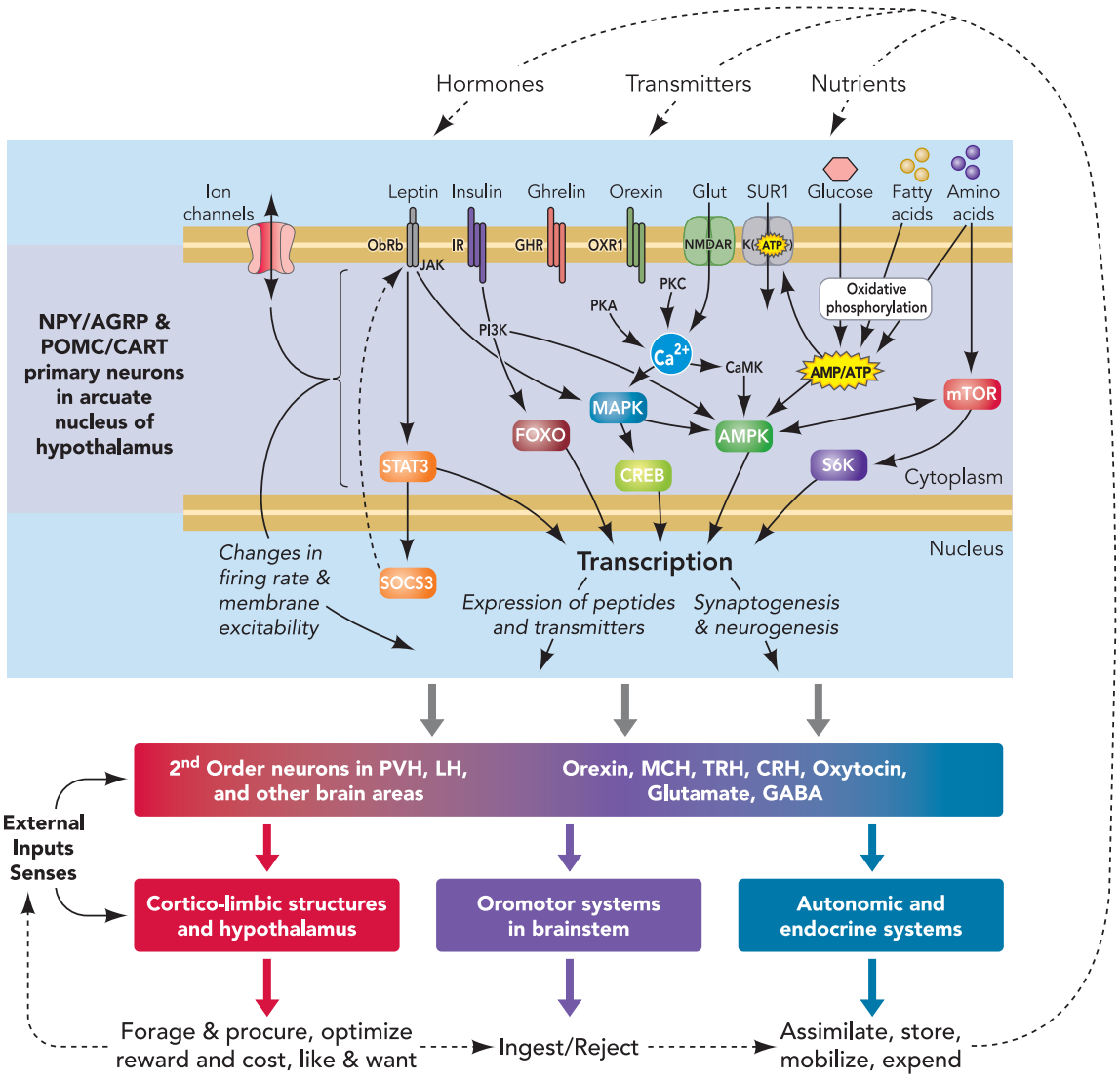

FIGURE 3. **Hypothalamic regulator of energy balance**
Highly schematic diagram depicting the major purported intracellular signaling pathways in a hypothetical arcuate nucleus neuron that integrates nutrient, hormonal, and neurotransmitter signals and activates downstream neural networks leading to behavioral, autonomic, and endocrine responses. ObRb, long form of leptin receptor; IR, insulin receptor; GHR, ghrelin receptor; OXR1, orexin-type-1 receptor; Glut, glutamate; NMDAR, NMDR-glutamate receptor; SUR1, sulfonylurea receptor; JAK, janus kinase; AMPK, adenosine monophosphate-dependent kinase; mTOR, mammalian target of rapamicin; PKA, protein kinase A.

information from brain areas associated with reward, motivation, learning, and memory and from brain stem areas associated with vagal and visceral sensory input, sensorimotor coordination, and arousal. In turn, these peptidergic second-order LHA neurons project widely through the entire brain (11), from the cortex to the spinal cord (FIGURE 4).

Second-order neurons in the PVH are classically associated with autonomic and neuroendocrine functions. Thyrotropin-releasing hormone (TRH) and corticotropin-releasing hormone (CRH) neurons receive direct input from both types of ARC neurons and regulate the thyroid and HPA axis and stress response, respectively (45).

In addition to the LHA and PVH, arcuate POMC/CART neurons also project to other brain areas. For example, leptin-sensitive POMC neurons project directly to brain stem areas associated with the response to satiety signals and autonomic outflow (13, 93).

What is homeostatic regulation?

The hypothalamic neurocircuitry discussed above is crucial to energy homeostasis as indicated by the development of obesity or leanness after loss- or gain-of-function manipulations of its main components. Although this circuit is assumed by many to regulate body weight and adiposity within a narrow set point, much like a thermostat controls room temperature, this view has been largely abandoned in favor of a more flexible regulator that can learn from past experience and adapt to changing environmental factors. Arguably, the major force "designing" the system was the constant struggle throughout evolution to find enough food for survival, resulting in a very strong defense of the lower limits of adiposity. One school of thought is that, over the millions of years of evolution, genes optimizing foraging and fuel efficiency were selected at least in some populations (66). Clearly, evolutionary pressure has also existed to limit the upper limits of adiposity and, perhaps more likely, body weight (78). Disadvantages of elevated body weight are particularly evident in birds and in becoming prey because of slower running speed.

Cortico-Limbic Pathways Coordinate Metabolic Need with the External World

It is clear that the neurocircuitry originating from the primary energy sensors in the arcuate nucleus

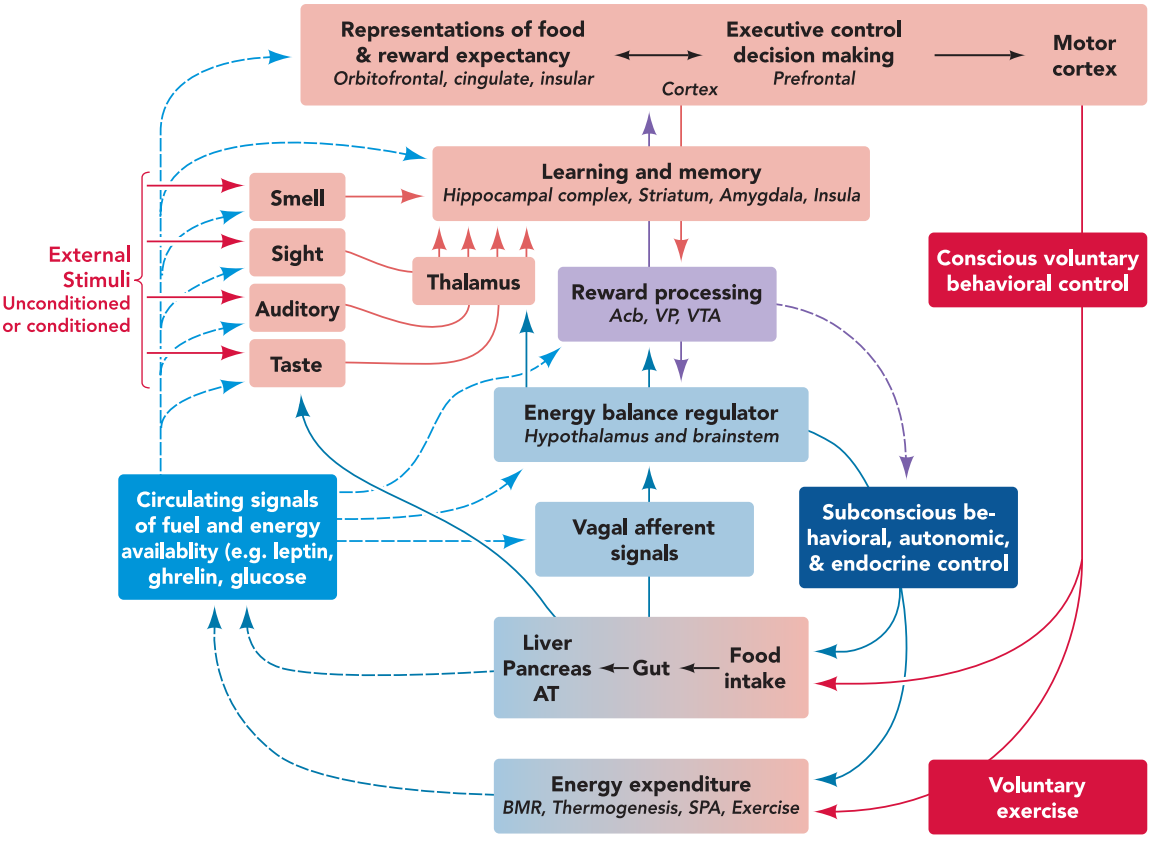

FIGURE 4. **Major systems and pathways responsible for the neural integration of internal and external information in the control of appetite and energy expenditure**
Blue areas and pathways are mainly involved in metabolic and energy balance regulation. Red areas and pathways are mainly involved in communication with the external world through cognitive and emotional processes such as learning and memory, reward, mood, stress, choice, and decision making.

described above is embedded in a much larger neural system that allows adaptation and coordination of metabolic needs to the demands and intricacies of the prevailing environment. For example, it does not make sense for the hungry vole to leave the burrow if the weasel waits outside. In fact, much of the brain has evolved to take care of hunger ever since mobile life forms emerged. Although procuring food in our modern environment is as easy as grabbing a piece of birthday cake on the table, it used to be a demanding task for most of the last 5 million years. Even more primitive invertebrate animals such as honey bees and ants use elaborate navigation and communication strategies to secure food sources and guarantee survival (30, 70, 85).

"Although humans have the ability to make conscious, voluntary decisions and choices, most of our actions have a subconscious component that escapes voluntary control."

Representations of experience with food

We remember past experiences with foods, particularly if the experience was out of the ordinary. Experiences that evoked either extreme pleasure or complete disgust generate the most salient memories. Thus we remember the restaurant and everything in and around it very well, where we had that extraordinary dish, and we remember even an average dish when we fell in love at that occasion. On the other hand, we immediately recognize and avoid a food that made us sick. A growing number of studies suggest that representations of experience with foods are generated in the orbitofrontal cortex, an area in the prefrontal cortex that receives converging information through all sensory modalities (FIGURE 4) (83). Therefore, representations contain a number of sensory attributes, including shape, color, taste, and flavor, as well as links to time, location, social context, cost, and reward expectation (25, 83).

It is not clear how and where exactly such representations are stored. The orbitofrontal cortex is in intimate contact with other cortical areas, particularly the anterior cingulate, perirhinal, and entorhinal cortices, as well as with the hippocampal formation and the amygdala, often collectively referred to as paralimbic cortex (for review, see Ref. 83). It is within these areas that polymodal representations are thought to be available as working memory for constant updating.

Reward and emotions

It is thought that emotions evolved as a mechanism to reinforce beneficial and suppress potentially harmful stimuli and behaviors. For example, the sweet taste of certain foods is associated with positive emotions that augment the motivational drive to obtain such foods; in brief, it is said to be rewarding. The reward value of a particular food is bundled with the other attributes into the stored representations discussed above. Thus life is all about learning how specific behavioral responses or actions lead to positive emotions or reward in the future. However, reward is a fuzzy psychological construct and is neurologically ill-defined. Berridge has proposed parsing reward into liking, wanting, and learning, each representing separate but interlinked psychological processes with distinguishable underlying neurological substrates (10).

Liking is also known as hedonic value of a food stimulus. Its most primitive form of expression is the characteristic "happy face" expressed by rodents, primates, and humans when tasting sweets. Current knowledge suggests that liking is neurologically organized by a widely distributed system with the mu-opioid and perhaps the cannabinoid receptor systems playing common denominators (19). Since the "happy face" is observed in decerebrate rats and anencephalic human infants, neural circuits in the hindbrain appear to be sufficient for the basic expression of liking (36, 79). In addition, areas in the ventral striatum and the amygdala are undoubtedly part of this distributed neural network of liking. 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 (42).

Wanting, or incentive salience, is another component of reward as proposed by Berridge (9, 10). It usually, but not always, follows liking. Although liking is closer to sensory processes, wanting is closer to motor action. Wanting can be further subdivided into decision-making and motor action. It can be shown that activity of the mesolimbic dopamine system accurately reflects the cue-driven inclination to choose one behavior over another to optimize reward. Neurologically, wanting is intimately linked to the mesolimbic dopamine system, which is crucial for the orchestration of motor behavior to obtain rewards. Dopaminergic projections from the ventral tegmental area to the nucleus accumbens and prefrontal cortex are the most important component of the implicit or unconscious "wanting" system (FIGURE 4) (24, 41, 89). Manipulation of this dopamine system powerfully influences wanting (instrumental performance for and consumption of) drugs or food but not "liking" (10, 16, 63, 88).

Metabolic signals modulate all levels of food-related cognitive and reward processing

It was originally thought that the classic nutritional feedback signals, such as leptin, insulin, gut hormones, and circulating nutrients themselves, act mainly on a few areas of the brain such as specific

parts of the hypothalamus and brain stem (see above). However, recent studies suggest that these metabolic signals have a much broader influence on brain functions (FIGURE 4).

For example, leptin has been shown to modulate food-related sensory input signals of all modalities, even at early stages of processing, so that low leptin levels can dramatically lower detection thresholds of external stimuli signaling availability of nutrients (35, 40, 75, 82). Leptin and insulin can also act directly on mesolimbic dopamine neurons to modulate wanting of food (29, 32, 37). Neural activity in the nucleus accumbens elicited by visual food stimuli is very high in genetically leptin-deficient adolescents and promptly returns to normal levels on leptin administration. While in the leptin deficient state, nucleus accumbens activation was positively correlated with ratings of liking in both the fasted and fed state; it was correlated only in the fasted state after leptin treatment and in normal individuals (28). The lower gut hormone PYY(3-36), which has now been convincingly demonstrated to suppress food intake in humans and rodents (17), also modulates activity of the ventral tegmental area (VTA) and ventral striatum (8). In contrast to leptin, the gut hormone ghrelin appears to facilitate foraging behavior and increase reward processing as part of its orexigenic action (1, 27, 39, 72).

Conscious decisions vs. subconscious drive

Although humans have the ability to make conscious, voluntary decisions and choices, most of our actions have a subconscious component that escapes voluntary control. This is why we eat palatable food such as chocolate in the absence of any metabolic need, even if we "know" better not to do it. The right prefrontal cortex appears to play a critical role in behavioral restraint and moral self-control by keeping reward-generating mechanisms in check (3, 46). The prefrontal cortex receives sensory information from inside and outside the body as well as emotional and cognitive information from the limbic system, and it is intimately connected to cortical areas involved in motor planning and execution. It is thus in an ideal position to translate all available homeostatic and environmental information into adaptive behavioral responses, in brief, to make choices and decisions (5, 59). Damage to the right frontal cortex can lead to a general disregard for the long-term adverse consequences of behavioral choices, such as increased risk taking and excessive food intake (3). A "Gourmand syndrome" with passion for eating highly palatable foods was reported in two case studies of humans with damage to the right frontal hemisphere (69, 81).

Modern neuroimaging studies also support the importance of a balanced control by distinct areas of the prefrontal cortex in the control of food intake. Successful dieters who have significantly higher levels of dietary restraint to nondieters show increased neural activity in the right dorsolateral prefrontal cortex in response to food consumption (26). In contrast, obese subjects show less activation of the left dorsolateral prefrontal cortex in response to food (44), and patients suffering from the Prader-Willi syndrome, who show severe disturbances in appetite control resulting in hyperphagia and obesity, show increased activity in the ventromedial prefrontal cortex when viewing pictures of food after glucose consumption (52). This latter finding is consistent with a role of the ventromedial prefrontal cortex in the mediation of food intake driven by conditioned (learned) motivational cues in sated rats (64).

Conclusions and Perspectives

The neural systems conferring the basic drive to eat are powerful, distributed, and redundant, and have been relatively refractory to pharmacological intervention and prevention of obesity. This is because in most obese people there is not one identifiable single defect in this system that could be corrected by drugs. Rather, there is a mismatch between the "thrifty" evolution of a large number of genes and their products and the current environment of plenty and sedentary lifestyle. Thus it is unlikely that mono-therapies, only acting on one single step in one pathway, will be successful in fighting the obesity war. Combination therapies acting on several steps in several pathways and involving lifestyle changes look more promising. Currently, the most effective treatment for morbid obesity is surgery, and it appears that Roux-en Y gastric bypass surgery "works" by favorably changing the physiological cross talk between the gut and the brain rather than through mechanical hindrance and malabsorption. So, unexpectedly, this procedure may help us understand what the critical pathways are that need to be simultaneously manipulated to trick the wisdom of the body.

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