Feeding Behavior in Mammals Including Humans

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The complex control of food intake and energy metabolism in mammals relies on the ability of the brain to integrate multiple signals indicating the nutritional state and the energy level of the organism and to produce appropriate responses in terms of food intake, energy expenditure, and metabolic activity. Central regulation of feeding is organized as a long-loop mechanism involving humoral signals and afferent neuronal pathways to the brain, processing in hypothalamic neuronal circuits, and descending commands using vagal and spinal neurons. Sensor mechanisms or receptors sensitive to glucose and fatty acid metabolism, neuropeptide and cannabinoid receptors, as well as neurotransmitters and neuromodulators synthesized and secreted within the brain itself are all signals integrated in the hypothalamus, which therefore functions as an integrator of signals from central and peripheral structures. Homeostatic feedback mechanisms involving afferent neuroendocrine inputs from peripheral organs, like adipose tissue, gut, stomach, endocrine pancreas, adrenal, muscle, and liver, to hypothalamic sites thus contribute to the maintenance of normal feeding behavior and energy balance. In addition to transcriptional events, peripheral hormones may also alter firing and/or connection (synaptology) of hypothalamic neuronal networks in order to modulate food intake. Moreover, intracellular energy sensing and subsequent biochemical adaptations, including an increase in AMP-activated protein kinase activity, occur in hypothalamic neurons. Understanding the regulation of appetite is clearly a major research effort but also seems promising for the development of novel therapeutic strategies for obesity.

Key words: energy metabolism; food intake; neuropeptide; adipokine; obesity

Introduction

The control of food intake and energy metabolism is a very complex process that depends on the ability of the brain to receive and integrate a wide range of signals indicating the nutritional state and the energy level of the organism and to produce appropriate responses in terms of food intake, energy expenditure, and metabolic activity.1 Central regulation of food intake is organized as a long-loop mechanism involving humoral signals and afferent neuronal pathways to the brain, processing in hypothalamic neuronal circuits, and descending commands using vagal and spinal neurons.2 Several brain regions have been involved in the control of energy homeostasis, but the
The Hypothalamic Integration Centers

In the hypothalamus, five specific areas, namely arcuate (ARC), paraventricular (PVN), ventromedial (VMH) and dorsomedial (DMH) nuclei, and lateral hypothalamic area (LHA), contain peptidergic neurons (Fig. 1) with either orexigenic or anorexigenic actions (Table 1). The ARC contains two main populations of neurons related to energy regulation, which express either the orexigenic neuropeptide Y (NPY) and agouti gene-related peptide (AgRP) or the anorexigenic neuropeptides proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). The PVN is a site where numerous neuronal
### TABLE 1. Main Orexigenic and Anorexigenic Molecules

<table>
<thead>
<tr>
<th>Orexigenic Neuropeptide</th>
<th>Anorexigenic Molecule</th>
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<tr>
<td>Neuropeptide Y</td>
<td>α-Melanocytostimulating hormone</td>
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<tr>
<td>Agouti-related peptide</td>
<td>Cocaine- and amphetamine-related transcript</td>
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<td>Melanin-concentrating hormone</td>
<td>Corticotrophin-releasing hormone</td>
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<td>Orexins/hypocretins</td>
<td>Leptin</td>
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<td>Galanin</td>
<td>Insulin</td>
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<td>Ghrelin</td>
<td>Serotonin</td>
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<tr>
<td>Endocannabinoids</td>
<td>Peptide YY</td>
</tr>
<tr>
<td>Excitatory aminoacids</td>
<td>GABA</td>
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<tr>
<td>(glutamate)</td>
<td>Glucagon-like peptide-1</td>
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<tr>
<td>Endogenous opiates</td>
<td>Cholecystokinin</td>
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<td>26RFa</td>
<td>Octadecaneuropeptide</td>
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<td>Catecholamines</td>
<td>Estradiol</td>
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<td>Neurotensin</td>
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<td>Urocortin</td>
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Pathways implicated in energy balance converge, including major projections from the ARC NPY neurons and others containing orexins/hypocretins, the POMC derivative α-melanocytostimulating hormone (α-MSH), and the appetite-stimulating peptide galanin. The VMH is a key target for the adipokine leptin, which acts on the hypothalamus to inhibit feeding and stimulate energy expenditure, and also receives inputs from cells in the ARC and from other brain centers implicated in feeding. The DMH, which has extensive connections with other medial hypothalamic nuclei and the lateral hypothalamus, is thought to serve as an integrative center processing information from neuronal populations in these sites and, like the VMH, is also a target of leptin. The LHA includes two sets of neurons expressing either melanin-concentrating hormone (MCH) or orexins/hypocretins. It also contains numerous fiber systems projecting to and from the medial hypothalamus and glucose-sensitive neurons that are stimulated by hypoglycemia. The perifornical part of the LHA, surrounding the longitudinal fiber bundle of the fornix, is innervated by POMC neurons and contains a high density of NPY receptors and, like the adjacent PVN, is highly sensitive to the hyperphagic effect of locally injected NPY (reviewed in Refs. 1 and 3).

### Central Molecular Mechanisms in Feeding Behavior

NPY, a potent orexigenic neuropeptide, is widely distributed in both the central nervous system (CNS), including the hypothalamus, and the peripheral nervous system (see Fig. 1). Under normal conditions, NPY-expressing neurons in the rodent hypothalamus are essentially confined to the ARC and send dense projections to other hypothalamic nuclei, particularly the PVN, DMH, and LHA. In addition, the PVN is the hypothalamic center receiving medullary adrenergic neurons that cocontain NPY. A subpopulation of ARC NPY neurons expresses leptin receptors (LR) and specifically the long isoform LRβ, the most important in mediating feeding control in response to variations of circulating leptin levels. The ARC NPY neurons are therefore hypothalamic targets for leptin; inhibition of the synthesis (and presumably release) of NPY seems to explain, at least in part, the ability of leptin to induce hypophagia and weight loss. Insulin, like leptin, also inhibits hypothalamic NPY gene expression. Conversely, ARC NPY neurons are activated by ghrelin, an orexigenic hormone mainly secreted by the stomach. NPY neurons also have extensive neural routes of communication with other hypothalamic regions and specific neuronal populations involved in energy homeostasis, including reciprocal connections with systems that inhibit eating (e.g., corticotrophin-releasing factor (CRH) neurons in the PVN, POMC neurons in the ARC, and serotonergic neurons in the raphe nuclei of the midbrain), and other systems that stimulate eating (e.g., the MCH and orexin/hypocretin cell populations of the LHA). NPY is among the
most potent orexigenic substances, mainly via the Y1- and Y5-receptor subtypes, and is a powerful stimulator of feeding when injected into the PVN and perifornical LHA of rodents. Interestingly, hyperphagia is accompanied by inhibition of the sympathetic outflow to brown adipose tissue and other thermogenic tissues, leading to a fall in energy expenditure and a shift toward positive energy balance. Moreover, increased hypothalamic NPY neuronal activity is present in a range of conditions characterized by weight loss and increased hunger, such as food restriction and fasting, insulin-deficient diabetes, and lactation, especially when mild food restriction is superimposed. ARC NPY neuronal activity is increased in the leptin deficient ob/ob mouse and the fa/ fa Zucker rat (with LR dysfunction), comparable to the changes seen in states of energy deficits in which leptin levels fall and fat mass is depleted. AgRP, another orexigenic peptide, is mainly expressed by NPY neurons in the ARC where it is inhibited by leptin and stimulated after fasting. AgRP acts through one or more (MC4-R, MC3-R, and even through MC1-R) of the five distinct melanocortin (mR) receptors and appears to be an inverse agonist of MC4-R, which is constitutively active and is predominantly expressed in the brain. AgRP expression is increased in ob/ob mice, in LR defective db/db mice, and in fasted wild-type mice (reviewed in Ref. 14). AgRP shows both acute and long-term effects on food intake, influences energy expenditure and thermogenesis, and seems to be involved in food selection, specifically enhancing the intake of high fat content diets (reviewed in Ref. 14). MCH is an orexigenic peptide produced by neurons of the LHA and the zona incerta, which receive input from ARC. Intracerebroventricular administration of MCH to mice and rats induces hyperphagia and decreases energy expenditure. Inhibition of MCH neurons results in hypophagia and leanness (reviewed in Ref. 14). Also orexins/hypocretins are orexigenic neuropeptides produced in neurons of the LHA and perifornical area that project to areas regulating feeding behavior and neuroendocrine homeostasis. The activity of orexin/hypocretin neurons is influenced by the feeding status, being increased by low glucose levels and decreased by signals related to nutrient ingestion. Orexin/hypocretin neurons in the LHA receive innervation from the POMC and NPY/AgRP neurons of the ARC, express their receptors as well as LRb, and project back to POMC and NPY neurons where they, like leptin, inhibit POMC neurons and activate NPY neurons (reviewed in Ref. 14). The neuropeptide galanin is mainly found in the ARC and LHA areas and is expressed in neurons that possess LRs. Galanin stimulates feeding, especially fat intake, inhibits insulin secretion, and induces hyperglycemia (reviewed in Ref. 14).

The effects of anorexigenic POMC-derived MC peptides are mainly mediated by MC4-R and MC3-R, which are expressed in several hypothalamic nuclei. To be more specific, MC4-R is expressed in the PVN and LHA and holds high affinity for \( \alpha - \text{MSH} \). Infusion of \( \alpha - \text{MSH} \) in the brain results in a decreased food intake and increased energy expenditure in rodents, which can be prevented by administration of a MC3-R/MC4-R antagonist. The anorexigenic peptide CART is expressed in different hypothalamic nuclei (ARC, PVN, DMH, LHA). It is co-expressed with POMC in the ARC, with MCH in the LHA, and with galanin in the PVN, thus showing colocalization with both orexigenic and anorexigenic neuropeptides. Central administration of CART leads to an inhibition of normal and NPY-induced food intake in rodents; in addition, chronic administration of CART decreases food intake and body weight, whereas administration of CART antibodies increases food intake in rodents. Moreover, food deprivation induced a decrease in CART mRNA while leptin administration upregulated CART expression (reviewed in Ref. 14). Besides its well-known role in the hypothalamus–pituitary–adrenal axis, CRH is also a potent anorexigenic peptide acting...
downstream of leptin. Central administration or direct administration of CRH into the PVN inhibits nocturnal- and fasting-induced feeding. Leptin increases CRH expression and CRH neuron activity in the fed state while decreases CRH expression and CRH neuron activity in the fasted state (reviewed in Ref. 14). In addition to peptidergic systems, reduced appetite results also by antagonism of the endocannabinoid system, particularly via the CB-1 receptor.21 Animal studies show that orexigenic CB-1 receptors and anorexigenic MC4-R interact synergistically to regulate appetite,22 CB-1 receptors acting downstream from MC4-R signaling. The CB-1 antagonist rimonabant is also shown to inhibit enzymes involved in lipogenesis, thus also showing peripheral metabolic antagonistic effects.23

Peripherally Borne Regulators of Food Behavior

Almost all the important metabolic hormones target the hypothalamic nuclei associated with energy control (Table 1).24 In addition, nutrients, such as glucose and lipids, have been shown to act at the hypothalamic level. A role is also played by locally acting components, such as the uncoupling proteins25 and enzymes, such as carboxypeptidase E and protein tyrosine phosphatase-1B, which facilitate insulin action and metabolism of fat.26 Catalytic reactions and other cellular processes, e.g., lipid-sensing via transcription factors, such as peroxisome proliferator-activated receptors, induce peripheral adipocytes to release leptin, the pancreas to release insulin, and the enteronocrine cells to release amylin, which further signal the hypothalamic nuclei to initiate an anorexigenic signaling cascade involving CART, cholecystokinin (CCK), CRH, glucagon-like peptide-1 (GLP-1) and GLP-2, neurotensin, peptide YY (PYY), and also triggers the MC signaling pathway. These signals and presence of fat in the small intestine27 act to inhibit ghrelin production and provide negative feedback mechanisms to orexigenic activation. Peripheral lipids, such as the fatty acid oleoylthanolamides, produced in the duodenum and adipose tissue also act, via the vagus nerve, to induce satiety and to decrease body weight.28

Leptin is a 16 kDa protein mostly produced by white adipose tissue and secreted into the circulation. It crosses the blood–brain barrier through receptor-mediated mechanisms and activates LRs in CNS nuclei. As mentioned above, activation of LRs in the ARC reduces feeding behavior and increases metabolic expenditure which, in turn, favors negative energy balance. Plasma leptin concentration parallels adipose tissue mass and is substantially increased in the obese. LRs are encoded by a single gene in both rodents and humans.29 Six variants have been identified so far30, Lrb possesses the longest intracellular domain, is evolutionarily conserved among species, and, as mentioned before, specifically mediates energy homeostasis.31 In hypothalamic neurons, Lrb mediates the activation of the Janus kinase 2 (JAK2)-signal transducer and activator of transcription protein type 3 (STAT3)-suppressor of the cytokine signaling-3 (SOCS-3) pathway, the phosphoinositide-3-kinase (PI3K) pathway, and the mitogen-activated protein kinase complex/extracellular-regulated kinase pathway (MAPK/ERK).32 Ghrelin, a peptide hormone of 28 amino acids secreted by the stomach, represents an opposing signal to leptin since it increases feeding and adiposity and reduces metabolism.9 Like leptin, ghrelin produces these effects by acting on hypothalamic feeding systems.33 In fact, most ghrelin effects can be obtained by central administration.9 Two ghrelin receptor subtypes have been identified: the growth hormone secretagogue receptor-1a (the key receptor involved in feeding responses triggered by ghrelin) and -1b (GHSR 1a and 1b). Leptin and ghrelin receptors are both expressed throughout the hypothalamus and the CNS with considerable overlap. Colocalization of Lrb and GHSR 1a in hypothalamic NPY neurons has been
observed, suggesting that leptin and ghrelin interact in these cells to maintain energy balance.34

**Energy Metabolism and Synaptic Plasticity**

Although transcriptional events have been described to support overall cellular alterations, recent evidence suggests that peripheral hormones may also alter firing and/or connection (synaptology) of neuronal hypothalamic networks in order to modulate feeding behavior. In particular, the two critical components of the MC system, the orexigenic NPY neurons and the anorexigenic POMC neurons, both respond to peripheral hormones in an acute fashion in slice preparations. Thus, firing of POMC cells is enhanced by leptin via both presynaptic and postsynaptic modes of action,35 whereas firing frequency of NPY neurons is diminished by leptin.36 Ghrelin, however, has been reported to enhance the firing rate of NPY neurons via a direct mechanism, whereas it diminished the frequency of action potentials of POMC cells predominantly by a presynaptic mode of action.37 Insulin also affected neuronal firing in the MC.38 Interestingly, the hypothalamus retains plasticity throughout life and immature synapses can frequently be found in the adult hypothalamus. Recent observations suggest that synaptic plasticity, which is also under the control of estradiol,39 may be a regulatory component in the hypothalamic control of energy balance. Leptin replacement in ob/ob mice indicated that synaptic rearrangement of feeding circuits is part of an ongoing general phenomenon. Furthermore, robust effects of peripheral ghrelin injections on the input organization of POMC neurons of mice led to wiring different from that induced by leptin.40 In addition, leptin markedly regulated the synaptic organization of lateral hypothalamic orexin/hypocretin neurons41 and ghrelin produced a rapid effect on synaptic formation in the hippocampus.42

**Fuel Sensing and Energy Balance**

Some observations suggest that intracellular energy sensing and subsequent biochemical adaptations occur in hypothalamic neurons; particularly those in the ARC and VMH directly respond to body metabolic fuels.43 One of these mechanisms includes an increase in AMP-activated protein kinase (AMPK) activity in response to an increase in the ratio of AMP/ATP.44 The activation of AMPK favors cellular responses generated to increase ATP levels, including increases in the synthesis and uptake of glucose and fatty acid oxidation by most cells, and, concomitantly, it inhibits ATP consuming processes, such as protein synthesis. Hypothalamic neurons have a similar nutrient-sensing mechanism.45 Thus, fasting or treatment with 2-deoxy-D-glucose increases the activity of AMPK in the hypothalamus.46 Hypothalamic cells are also sensitive to circulating free fatty acids, again likely mediated by AMPK.46 Free fatty acids diffuse into hypothalamic neurons and are esterified and transferred into the mitochondria for oxidation, which ultimately leads to increased feeding.47 Moreover, recent findings support a role for hypothalamic fatty acid metabolism in the regulation of food intake and, in particular, that this mediates the orexigenic effects of ghrelin.48 The activation of AMPK may also gate hypothalamic responses to peripheral hormones as well, given that leptin decreases and ghrelin increases hypothalamic AMPK activity.49

**Regulation of Feeding Behavior in Humans**

**Genetic Obesity**

Opposite to what has been extensively found in rodents, genetic obesity is very infrequent in humans. Moreover, exogenous administration of regulatory peptides—including leptin—did not lead to the relevant results expected on the basis of animal experiments. Still, during the
last few years severe human obesity has occasion-
ally been identified as dependent on several single-gene defects involving molecules identi-
tical or similar to those identified as a cause of obesity in rodents.\textsuperscript{50} Mutation in the same gene, despite often causing very similar physio-
logical changes, usually is different in terms of phenotypic differences between humans and experiment-
al animals. With respect to leptin deficiency, for instance, in the last decade a few severely obese subjects with a homozygous mutation in the \textit{ob} gene (G133), as well as others carrying a homozygous missense mutation truncating the protein,\textsuperscript{51} were described. All of them had severe early-onset obesity and marked hyperpha-
gia\textsuperscript{52} often accompanied by hyperinsulinemia, hypogonadotropic hypogonadism, lower rest-
ing energy expenditure, blunted sympathetic-dependent thermogenesis, and severe T cell number and function changes, consistent with high rates of childhood infection morbidity and mortality. Still, not all features of \textit{ob}/\textit{ob} mice are present in human leptin-defective sub-
jects, especially in terms of growth retardation or hypothalamic–pituitary–adrenal axis activa-
tion. Yet, extremely important are the dramatic effects of chronic treatment with daily subcu-
taneous injections of leptin in reducing body weight and fat mass in such cases,\textsuperscript{53} even at doses causing plasma leptin levels as low as 10\% of those predicted by height and weight. These results came along with normalization of hyperphagia, a stable increase resting/activity-
related energy expenditure, appropriate pu-
bertal development, and enhanced thyrotropin pulsatility and thyroid hormone secretion.\textsuperscript{54} In case of missense mutations, anti-leptin antibod-
ies were observed as an adverse effect of treatment and were inconsistent in nature, possibly from immune function deficiency.\textsuperscript{55} Interest-
ingly, hormone replacement treatment shifted the cytokine secretion pattern from Th2 to Th1, which enhances antibody production.

A homozygous mutation truncating \textit{LR}s be-
fore the transmembrane domain was also iden-
tified as a genetic defect eventually underlying a phenotype similar to that of leptin deficiency but displayed impaired basal and stimulated growth hormone secretion, decreased insulinnlike growth factor (IGF)-1, and evoked hypotha-
lamic hypothyroidism.\textsuperscript{55} When dealing with POMC, homozygous or compound heterozygous mutations implying POMC deficiency were described as well as mutations causing inactive POMC secretion or disrupting correct POMC processing.\textsuperscript{56,57} Such cases developed hyperphagia and early-
onset obesity (presumably from impaired MC signaling in the hypothalamus) together with adrenal deficiency from blunted corticotrophin (ACTH) release, pale skin, and red hair from lacking the MSH signal. Something similar has been observed when the gene encoding the pro-
hormone convertase 1 (PC1), which is involved in POMC processing, contains mutations re-
sulting in incorrect POMC cleavage.\textsuperscript{58} More frequently MC4-R, the receptor most closely linked to control of energy balance, is absent or altered in humans, thus causing dominantly in-
erited obesity (homozygotes being more obese than heterozygotes). Similar to what is observed in knockout mice, codominance, with modula-
tion of expressivity and penetrance of the phe-
notype, seems to best describe the mode of in-
eritance, and the phenotype is characterized by increased lean mass (opposite to leptin defi-
cient subjects), faster linear growth, and higher insulin levels (reviewed in Ref. 59).

The Pleasure of Food

In humans, appetite results from a series of inputs that mostly relate to psychology rather than biology, with hedonic, emotional, and cognitive factors variably interplaying in energy balance. To be more specific, mnemonic representations of experience with food re-
sult from continuous information exchanges among orbito-frontal and prefrontal cortex, anterior-cingulated insular perirhinal and en-
torhinal cortices (involved in olfactory- and taste-specific satiation), as well as hippocampus and amygdala (i.e., paralimbic cortex), which in
turn are influenced by ghrelin, obestatin, and leptin, all mainly acting on the hippocampus and unexplainedly influencing spatial memory in the same way. On the other hand, reward from palatable food comes through the nucleus accumbens and ventral pallidum in the ventral striatum (VS), the midbrain dopaminergic ventral tegmental area (MDVTA), the prefrontal cortex, the amygdala, and the hippocampus. Leptin and ghrelin mostly act, in an opposite way, on the MDVTA and the nucleus accumbens, while PYY and GLP-1 stimulate the VS and MDVTA. Gustatory signals, often enhanced by nutrition-related vagal afferents, preferentially project upon amygdala and insular cortex, while circulating lipid levels influence MDVTA through galanin, enkephalin, dynorphin, and orexins/hypocretins, which also, opposite to leptin, enhance food-smelling abilities. All such information is substantially derived from animal studies, but quite recently functional magnetic resonance brain scanning was used to investigate sensory-specific satiation and showed that the regulation of chocolate ingestion may vary between genders. On the other hand, it is known that women eat less during the peri-ovulatory period and preferentially eat sweet food during the luteal phase and that elderly people have less appetite than young people from not only decreased energy expenditure but also from ill-defined mechanisms potentially involving sex–steroid balance as well as altered CNS signaling to and from peripheral organs. A typical condition characterized by anorexia in the human is cancer, with central and peripheral neurohormone–dependent decreased food smell/taste together with early satiety contributing to it; once again, the inner mechanisms involved are still a matter of debate, and one can only hypothesize some steroid-dependent appetite regulation from the positive effect of megestrol administration in 25% of patients.

When dealing with circulating signals, women with constitutional thinness display higher levels of PYY and leptin (both anorexigenic) and lower concentrations of GLP-1 (anorexigenic, yet enhancing insulin secretion) and ghrelin (orexigenic) than women with anorexia nervosa, thus showing that these two conditions, so markedly distinguished in terms of appetite and feeding behavior, differ substantially in their food-regulating hormonal balance.

**Present and Potential Therapy Targets in Terms of Food Intake**

Regardless of the intimate mechanisms regulating appetite in humans, some drugs have proven beneficial to obese patients, according to animal-based data, and many others are in the pipeline or under speculation. Therefore, in our view food intake regulation may be properly investigated in humans by simply following the old-fashioned, still-practical, “ex juvantibus” approach. That is why, when dealing with feeding behavior, we prefer to talk about physiological data learned through pharmacology. One way to help obese subjects is to increase catabolism. In principle this might be obtained by giving leptin to the obese, but, as mentioned before, only the rare cases of genetic obesity with leptin deficiency would benefit. More easily, one can go back to the insulin-sensitizing agent metformin, which is mainly meant for normalizing glucose levels in diabetic subjects but is also endowed with some anorexigenic properties linked to peripheral signals originated by gastrointestinal discomfort and to yet ill-defined metabolic effects related to the activation of the glucolytic cascade at the hypothalamic level. Only peripheral effects seem to be involved in the mild anorexigenic properties of orlistat, an agent interfering with gut triglyceride absorption and causing steatorrhea in the case of lipid-rich diets. Another possibility comes from the modulation of serotonin release, which selectively decreases carbohydrate intake and is also involved in mood amelioration. After years of disillusion coming from a series of sometimes serious adverse effects, we now have a
strong and safe enough drug in our hands, provided it is used appropriately, called *sibutramine*. This substance inhibits both serotonin and noradrenaline reuptake at hypothalamic nerve terminals, thus acting upon the drive for carbohydrates through serotoninergic signal modulation while enhancing thermogenesis centrally and lipolysis at the level of the adipose tissue; some adverse effects might be expected for users, though, both minor, such as headache, dry mouth, or constipation, and serious, such as a clinically relevant increase in blood pressure and/or heart rate, requiring careful monitoring and sometimes immediate drug withdrawal.67 Rimonabant, a strong CB-1 receptor antagonist, is a recently developed promising drug that acts peripherally through retrograde suppression of endocannabinoid signaling both at the peripheral level (muscles, adipose tissue, liver, and gastrointestinal tract) and within the CNS (hypothalamus and nucleus accumbens). It is therefore acting both on appetite and on motivation for palatable food, thus approaching obesity from a wide-field point of view.68 Several studies have been carried out on rimonabant, all providing evidence for a strong and sustained inhibition of appetite, granting long-term weight loss, and with a series of beneficial effects on many cardiovascular risk factors associated with the metabolic syndrome.69–71 The mechanism of action of rimonabant is intrinsically nested with the risk for severe depression—sometimes leading even to suicide attempts—so that an accurate selection of patients to be treated is mandatory, and at the moment even the current use of antidepressants is considered as a contraindication to this drug.

Many other drugs are in the pipeline at the moment and some are just thought of as a possible approach to appetite regulation. Among them the ciliary neurotrophic factor (CNTF) should be cited, which in hypothalamic feeding centers induces proliferation of neurons that contain leptin-responsive elements thus enhancing body weight reduction; in fact, a CNTF agonist would be of great benefit in the field.72 Attempts to modulate various Y-receptor subtypes in order to counteract NPY-induced feeding have been unsuccessful to date, and research keeps an extremely prudent attitude with this because Y-receptors are generally involved in many other physiological functions, which would be lost with administration of an effective anti-NPY drug.73 Research has been focused for years on potential effects of ghrelin receptor blockers, the most clinically useful application of which is thought to be weight regain prevention after weight loss.

Another possible new approach for the future is the modulation of MC4-R through specific agonists endowed with longer effect (also exploiting gene therapy). At the moment a series of unexpected effects has been described, including penile erections and flushing, hypotension, lower response to pyrogens, and anti-pain effect, which might even interest the drug industry in their use for erectile dysfunction and other pathologic conditions.74

### Conclusions

According to the above-reported information, understanding the complex control of appetite is an enormous undertaking requiring meticulous research of discrete peptide and sympathetic pathways, receptor–ligand interactions and properties, transmission conditions and effects, and intracellular–extracellular components involved in stimulatory and inhibitory appetitive responses. The integration of such complex data, however, also appears promising in the perspective of novel therapeutic strategies for obesity and the metabolic syndrome, two health issues reaching epidemic proportions.

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Conflicts of Interest
The authors declare no conflicts of interest.

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