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REVIEW

Neuroendocrine control of food intake

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Abstract Appetite is regulated by a complex system of central and peripheral signals which interact in order to modulate the individual response to nutrient ingestion. Peripheral regulation includes satiety signals and adiposity signals, while central control is accomplished by several effectors, including the neuropeptidergic, monoaminergic and endocannabinoid systems. Satiety signals, including cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), originate from the gastrointestinal (GI) tract during a meal and, through the vagus nerve, reach the nucleus tractus solitarius (NTS) in the caudal brainstem. From NTS afferents fibers project to the arcuate nucleus (ARC), where satiety signals are integrated with adiposity signals, namely leptin and insulin, and with several hypothalamic and supra-hypothalamic inputs, thus creating a complex network of neural circuits which finally elaborate the individual response to a meal. As for the neuropeptidergic system, ARC neurons secrete orexigenic substances, such as neuropeptide Y (NPY) and agouti-related peptide (AGRP), and anorexigenic peptides such as pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). Other brain areas involved in the control of food intake are located downstream the ARC: among these, the paraventricular nucleus (PVN), which produces anorexigenic peptides such as thyrotropin releasing hormone (TRH), corticotrophin releasing hormone (CRH) and oxytocin, the lateral hypothalamus (LHA) and perifornical area (PFA), secreting the orexigenic substances orexin-A (OXA) and melanin concentrating hormone (MCH). A great interest in endocannabinoids, important players in the regulation of food intake, has recently developed. In conclusion, the present work reviews the most recent insights into the complex and redundant molecular mechanisms regulating food intake, focusing on the most encouraging perspectives for the treatment of obesity.

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Introduction

The prevalence of obesity is increasing worldwide. In the United States, it has increased from 22.9% to 30.6% over 7 years, and according to the National Health and Nutrition Examination Survey (NHANES), which reports data from 1999 to 2002, 29.8% of adults aged at least 20 years were overweight, 30.4% were obese and 4.9% were extremely obese [1]. The prevalence rates in other industrialized countries are similar, and developing countries adopting a “westernized” lifestyle are exposed to a dramatic increase of this disorder. Accordingly, obesity is now considered as a global pandemic with over 300 million adults affected worldwide [2]. As expected, the prevalence of obesity-related disorders has also increased: about 80% of obese adults have at least one and 40% two or more comorbidities including diabetes mellitus, hyperlipidemia, arterial hypertension, cardiovascular disease, gallbladder disease and some forms of cancer [3]. Approximately 300,000 deaths per year may be attributed to obesity [4]. A weight gain of 1 kg has been shown to increase cardiovascular risk by 3.1% and diabetes risk by 4.5–9% [5], while an 11% weight loss reduces cardiovascular disease and diabetes mortality by 25% [6]. Therefore, effective treatments for obesity are urgently needed.

This article will review the present knowledge on the central and peripheral pathways interacting in the regulation of eating behavior as well as the possible role of their alterations in the pathophysiology of obesity. In this context, some promising pharmacological strategies targeting anorexigenic and orexigenic signaling peptides will be described.

Meal onset and termination

Brain is the recognized coordinator of eating behavior. Meal onset, however, does not appear to be chiefly regulated by biochemical signals. According to the old “glucostatic theory”, the “feeding center”, located in the lateral hypothalamic area (LHA), perceived the inter-meal fall of blood glucose and stimulated food intake. The subsequent post-prandial hyperglycemia was believed to activate the “satiety center” in the ventromedial hypothalamus (VMH), which inhibited the “feeding center” with cessation of eating [7]. According to recent evidence, meal onset appears to be biochemically induced only in the case of serious energy deprivation, while usually it is controlled by social, cultural and

environmental factors strictly related to the lifestyle. The biochemical control of caloric intake is rather exerted on the termination of meal through a subtle modulation of meal size and sense of fullness, depending on energy requirements [8]. Such a sophisticated regulatory mechanism is controlled by the hypothalamus, which is continuously informed about the nutritional, energetic and environmental status of the body through peripheral and central orexigenic or anorexigenic messages. Peripheral messages include satiety and adiposity signals delivered by nervous inputs and gut peptides. The main central messages are conveyed by neuropeptides, monoamines and endocannabinoids.

Arcuate nucleus

The chief pathways regulating meal size are summarized in Figs. 1 and 2. Arcuate nucleus (ARC), adjacent to the third ventricle, is the chief hypothalamic area involved in the control of food intake and contains two interconnected groups of “first-order” neurons releasing neuropeptide Y (NPY) and agouti-related peptide (AGRP), which enhance food intake, and the anorexigenic substances pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). The axons of these neurons project to “second-order” neurons, located in part in the paraventricular nucleus (PVN), where the anorexigenic substances thyrotropin-releasing hormone (TRH), corticotropin-releasing hormone (CRH) and oxytocin are secreted, and in part in LHA and perifornical area (PFA), where the orexant molecules melanin-concentrating hormone (MCH) and orexins are produced. When adiposity signals reach ARC, anorexigenic peptides are released which activate a catabolic circuit. In contrast, the activation of anabolic pathway leads to the release of orexigenic peptides and occurs when adiposity signal

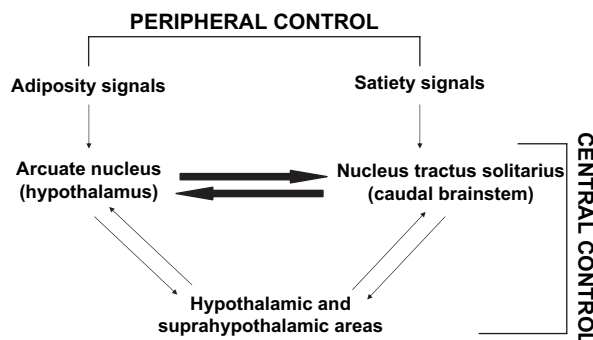


Figure 1 Control mechanisms of food intake.

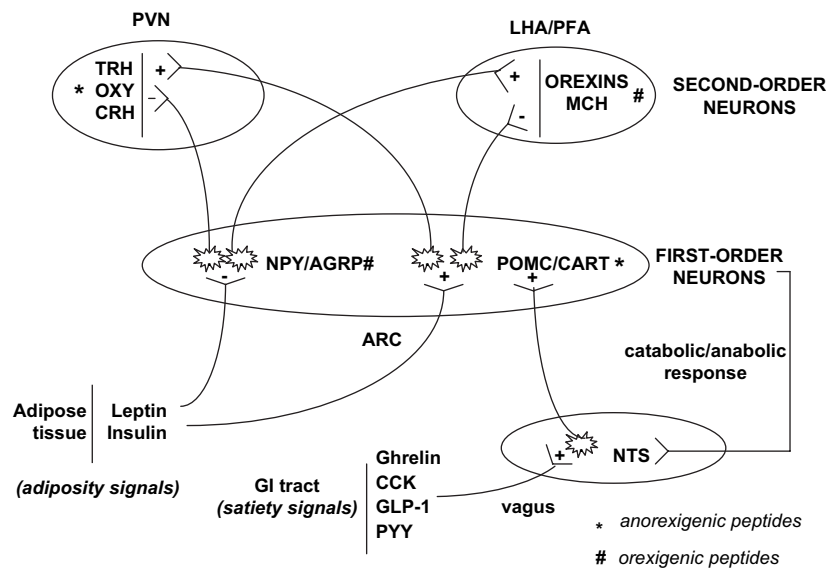


Figure 2 A schematic representation of the chief brain pathways involved in the regulation of eating behavior. ARC, arcuate nucleus; NTS, nucleus of the solitary tract; CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; PYY, peptide YY. PVN, paraventricular nucleus; LHA, lateral hypothalamic area; PFA, perifornical area; NPY, neuropeptide Y; AGRP, Agouti-related peptide; POMC, pro-opiomelanocortin; CART, cocaine- and amphetamine-regulated transcript; CRH, corticotropin-releasing hormone; TRH, thyrotropin-releasing hormone; OX, oxytocin; MCH, melanin-concentrating hormone.

concentrations in the brain are low, thus indicating the urgency to replenish fuel stores.

Satiety signals

Satiety signals are generated in the gastrointestinal (GI) tract during a meal and regulate food intake on meal-to-meal basis, inducing a sense of fullness. After entering the GI lumen, nutrients trigger the secretion of several peptides which, in addition to other actions, activate vagal and sympathetic pathways afferent to the nucleus of the solitary tract (NTS) in the caudal brainstem (Fig. 2) where they provide information on the chemical and mechanical properties of the nutrients [8]. NTS expresses both POMC and leptin receptors, which suggests that this brain area, like ARC, is able to integrate peripheral satiety and adiposity signals with hypothalamic and suprahypothalamic information [9]. These same peptides also reach the hindbrain via the bloodstream and interact with local receptors. The most important satiety signals are cholecystokinin (CCK), bombesin, glucagon, glucagon-like peptide-1 (GLP-1), GLP-2, apolipoprotein A-IV, amylin, somatostatin, enterostatin, and peptide YY(3–36) (PYY_{3–36}). Based on this knowledge, intensive pharmacological research is in progress in order to develop anti-obesity drugs.

CCK

CCK is secreted by duodenal and ileal cells when nutrients enter the lumen and binds to specific receptors (CCK-1R) located on vagal sensory terminals delivering to NTS a sense of fullness. Under some experimental conditions exogenous CCK elicits satiety and reduces meal size in different species [10,11]. Indeed, intravenous infusion of physiological doses of CCK-33 significantly reduced the size of a single-food test meal as well as the degree of post-prandial hunger in humans [12]. However, the CCK agonist cerulein failed to modify food intake both in lean and obese Zucker rats [13] and in obese women [14]. In contrast, intravenous infusion of loxiglumide, a CCK-1R antagonist, inhibited the satiating effect of intraduodenal administration of fat emulsions in healthy men [15] and the same drug was able to reverse the pre-meal reduction of hunger induced by CCK-8 to humans [10] (Table 1).

GLP-1

GLP-1 is another gut hormone released in response to food intake. It enhances glucose-induced stimulation of insulin synthesis and secretion, while suppressing glucagon secretion and delaying gastric emptying. Moreover, its infusion to rats decreases food intake and body weight [16]. In

Table 1 Antiobesity agents under investigation with GI peptides as targets (modified from Arbeeney [5])

Pharmacological target	Compound
PYY _{3–36} receptor agonists	<ul style="list-style-type: none"> • PYY_{3–36} (intranasal) • AC162352
GLP-1 agonists	<ul style="list-style-type: none"> • Exenatide (AC2993) • Exenatide-LAR (AC2993 LAR) • Liraglutide (NN2211) • BIM 51077 • AVE0010 • CJC-1131 • Albugon • TH0318 • GLP-1 gene therapy
Dipeptidyl peptidase IV inhibitors (antagonist of GLP-1 inactivators)	<ul style="list-style-type: none"> • Vildagliptin (NVP-LAF237) • MK431 • T6666/815541, 825964, 823093 • BMS 477119
CCK-A agonists	<ul style="list-style-type: none"> • 181771 • SR146131 • SR125180
Ghrelin action antagonists	<ul style="list-style-type: none"> • GHS-R antisense oligonucleotides (BIM 28163) • Anti-ghrelin antibodies • Peptide antagonists

a recent meta-analysis of seven studies, a significant dose-dependent decrease in *ad libitum* caloric intake was shown both in lean and obese subjects [17]. In these latter a diminished postprandial GLP-1 release has also been demonstrated [18–21]. These notions represent a rationale for the use of GLP-1 in the treatment of obesity and diabetes mellitus. Unfortunately, the clinical employment of this molecule is limited by its short half-life (1–3 min), since it is rapidly inactivated by the enzyme dipeptidyl peptidase IV (DPPIV). Long-acting GLP-1 agonists, as well as inhibitors of DPPIV, are under investigation to circumvent this limitation (Table 1). Intravenous infusion of exendin-4 (exenatide), a potent long-acting agonist of GLP-1, in healthy volunteers was followed by a 21% decrease in total daily food intake, as well as by a reduction in fasting and post-prandial glucose level [22]. Exenatide is now available on the market as an adjunctive therapy to improve glycemic control in patients with type 2 diabetes

mellitus treated with conventional oral antidiabetic drugs [22]. While some studies have shown a beneficial effect of DPPIV inhibitors on glucose metabolism in patients with type 2 diabetes mellitus, there is no evidence as yet on the efficacy of such drugs on weight loss in humans [23,24].

PYY

PYY_{3–36} is mostly released by L-cells of the distal segments of the gut in amounts correlated with the ingested calories [25]. Most, but not all, published data indicate that peripheral infusion of PYY_{3–36} reduces food intake and prolongs inter-meal intervals in several animal models [25–29]. Recently, a PYY_{3–36} deficiency has been demonstrated in obesity [29,30]. Peripheral infusion of doses of the peptide reproducing postprandial concentrations are able to significantly reduce caloric intake in obese as well as in lean subjects [25]. PYY_{3–36} is hypothesized to act at the hypothalamus, at least in part via vagal pathways afferent to NTS [30]. Its effect might be mediated by excitement of POMC neurons and activation of anorexigenic circuits [8]. Although PYY agonists are under active investigation (Table 1), further information is still needed about the relative contribution of PYY to satiety and its potential use for weight reduction.

Ghrelin

Ghrelin is the only orexigenic GI peptide isolated so far. This 28-amino-acid acylated peptide is mainly secreted by the “A-X like” cells of the oxyntic glands of the stomach and represents the chief endogenous ligand for growth hormone-secreting receptors (GHS-Rs) [31]. It is also synthesized by the placenta, kidney, heart, thyroid and Leydig cells. A mounting body of evidence has demonstrated that ghrelin, in addition to its powerful GH-releasing and orexant effects, plays a remarkable role in the control of ACTH and prolactin secretion, glucose and lipid metabolism, gastric motility and acid secretion, heart function, sleep, and reproduction. In addition, ghrelin exerts antiproliferative effects both *in vivo* and *in vitro* [31]. Ghrelin receptor (GHS-R1a) is chiefly located in the hypothalamus-pituitary unit, especially on the NPY and GHRH neurons [32]. In rats, ghrelin enhances food intake in a dose dependent manner. In humans, intravenous infusion of ghrelin at physiological doses induces hunger and causes short-term enhancement of food intake [33]. Circulating ghrelin increases almost two-fold just before a meal and rapidly falls down postprandially

[34]. Ghrelin levels are elevated in anorectic patients [35] and low in obese subjects [36]. In these latter, the negative feedback physiologically exerted by food on ghrelin release is lacking [37]. Notably, the reduction of caloric intake observed in obese patients following infusion of PYY_{3–36} is accompanied by a decrease in circulating ghrelin [25]. Interestingly, the only form of human obesity characterized by elevated circulating ghrelin described so far is the one associated with Prader–Willi syndrome [38] and a contribution of hyperghrelinemia to the hyperphagia of these patients has been suggested.

Ghrelin action is mediated by the enhancement of NPY/AGRP pathways and the inhibition of POMC neurons [32] in a way opposite to that of leptin (see below). Vagus nerve is likely to be an important mediator of ghrelin action [31].

Prolonged ghrelin administration to rodents is followed by an increase in fat mass and body weight, likely a result of decreased lipid oxidation [34]. Antagonists of ghrelin may be a potential approach to limit food intake and reduce fat mass in obesity (Table 1); however, the administration of the novel GHS-R1a antagonist BIM-28163 to rodents has led to a paradoxical weight gain accompanied to the expected inhibition of GH release [39]. Another peptide also derived from proghrelin and named obestatin has recently been isolated from rat stomach. Administered to rats, this peptide has been found to bind the orphan receptor known as GPR39, to suppress food intake and decrease body weight [40].

Adiposity signals: leptin and insulin

Leptin

Leptin, the *ob* gene product, is produced mainly in the adipose tissue and enters the brain in proportion to its plasma levels. Leptin maintains long-term control on adiposity and regulates adaptive metabolic changes in response to modifications of nutritional [42]. Leptin is also able to regulate short-term energy intake, modulating meal size according to changes in energy balance: with negative energy balance, low leptin signaling activates anabolic and inhibits catabolic circuits, enhancing NPY/AGRP release and blocking the activity of POMC/CART neurons with increase in meal size and decrease in energy expenditure [9]. The opposite occurs with positive energy balance. Genetic absence of either leptin or its receptor is associated with severe obesity and hyperphagia [41]. These features improve both in animal and human

models after restoration of physiological plasma leptin levels. An 18-month treatment with recombinant human leptin of adult leptin-deficient patients caused a weight loss greater than 40% and an initial 49% reduction of food intake [41]. Congenital leptin or leptin receptor deficiencies, however, are extremely rare in humans, and the beneficial effect of leptin in essential obesity appears to be only transient [11,42–44]. Most obese subjects display increased levels of circulating leptin, indicating obesity as a state of leptin resistance [45]. Elucidation of the molecular mechanisms underlying this alteration could provide clues for successful treatment of obesity.

Insulin

When body weight augments, insulin resistance occurs with attendant increase in insulin secretion. The hormone enters the brain in proportion to its circulating levels, contributing to reduce energy intake through the activation of catabolic pathways [9]. Central administration of insulin significantly reduces feeding and body weight in animal models [37]. Insulin and leptin both activate POMC neurons, but they seem to differentially regulate AGRP, with leptin inhibiting and insulin stimulating its synthesis [46]. In any case, insulin deficiency is associated with increased NPY, while insulin administration inhibits hypothalamic NPY expression [37]. Indirect and direct evidence suggests that the two adiposity signals, leptin and insulin, not always act in concert in regulating food intake [47].

Neuropeptidergic system

NPY

NPY is the most powerful central enhancer of appetite. Its expression is predominant in ARC, from which NPY neurons project to second-order neurons located in PVN, LHA, PFA, ventromedial (VMN) and dorsomedial (DMN) nuclei, and to other brain regions, setting in motion the anabolic pathway [48]. Furthermore, 90% of NPY neurons co-express AGRP [9]. Low leptin levels, hypoglycemia, hypoinsulinemia, and conditions of negative energy balance all enhance NPY mRNA expression in ARC. Central administration of NPY inhibits thermogenesis, enhances food intake and promotes adipogenesis in rats [49]. To date, six NPY receptors have been isolated, two of which (Y1 and Y5) seem to mediate the NPY anabolic effects. Y1 and Y5 antagonists are under investigation as

Table 2 Antiobesity agents under investigation with hypothalamic and supra-hypothalamic signals as targets (modified from Arbeeny [5])

Pharmacological target	Compound
NPY1 receptor antagonists	A number of compounds studied in vitro and in animal models
NPY5 receptor antagonists	A number of compounds studied in vitro and in animal models
MC4 receptor agonists	A number of compounds studied in vitro and in animal models
MCH receptor antagonists	• SB-568849
Dopamine and norepinephrine reuptake inhibitors	• Bupropion
Modified ciliary neurotrophic factor	• Axokine
Cannabinoid CB1 receptor antagonists	• Rimonabant • SR147778 • SLV319
5HT2c serotonin receptor agonist	• APD356

antiobesity agents (Table 2), although blockade of NPY activity might be associated with side effects such as arterial hypertension, analgesia, impairment of pituitary hormone secretion and hypoglycemia [50].

AGRP

AGRP is another potent orexigenic peptide. Its release by ARC is inhibited by leptin infusion, while its expression is upregulated in *ob/ob* leptin-deficient mice. AGRP influences food intake mainly through the competitive antagonism of central melanocortin receptors (see below) [51]. Alternative mechanisms of action might be mediated by orexin or opioid receptors [9]. AGRP secretion appears to be chiefly triggered by any impairment of energy balance [52]. High circulating levels of AGRP have been documented in human obesity [53], and a polymorphism in the human AGRP gene (c. 199G → A), which seems to be correlated with late-onset obesity, has recently been described [54].

POMC

POMC is the precursor of several molecules including α -MSH, which represents the main regulator of energy balance in this family. In rats, a body weight increase higher than 5% induced by involuntary overfeeding is followed by a significant increase in POMC expression and by anorexia. This pattern is reversed by intracerebroventricular administration of a melanocortin-receptor antagonist [9].

The anorexigenic effect of melanocortin is mediated by two receptors, MC3R and MC4R, highly represented in the brain and particularly in ARC.

In humans, more than 5% of the cases of morbid nonsyndromic obesity are associated with mutations of the MC4R gene. Heterozygous mutations are characterized by severe obesity, hyperphagia, increased fat free mass, hyperinsulinemia and acceleration of linear growth, while homozygous mutations exhibit an even more severe phenotype [55]. A mutation of the MC3R gene, responsible for obesity and insulin resistance, has recently been found in a child and his father [56].

The key role of the melanocortinergic system as a mediator of anorexigenic signaling is encouraging the experimental use of agonist or antagonist molecules for the treatment of eating disorders. Due to their long-lasting anorexigenic effect, some MC4R analogs, such as MTII [57], are good candidates as antiobesity drugs (Table 2). Syndecans are a family of four transmembrane heparan sulfate proteoglycans that act as coreceptors for a variety of cell-surface ligands and receptors. Interestingly, syndecan-1 and syndecan-3 enhance the activity of AGRP [58]. Thus, inhibitors of syndecan-3 have been proposed as a possible treatment of obesity and are now under investigation.

CART

Ninety percent of CART neurons are co-localized with POMC neurons in ARC and project to second-order neurons likely mediating the anorexigenic effect of leptin. The anorexigenic action of CART seems to be mediated by central release of GLP-1, since blockade of GLP-1 receptors inhibits CART-induced hypophagia [59].

Both *ob/ob* and *fa/fa* mice show reduced CART expression, while CART central administration dose-dependently reduces food intake in rats [37]. A missense mutation in the CART gene has recently been described, which causes severe obesity and reduction of resting energy expenditure in humans [60]. CART null mice develop increased

food intake and obesity while on a high fat diet, whereas, unexpectedly, food intake is reduced in the heterozygous model [62]. This suggests a dual effect of CART on eating behavior, likely dependent on different sites of action at the hypothalamus. Indeed, 95% of CART neurons located in the LHA co-express the orexigenic peptide MCH [61].

MCH

MCH is expressed in a discrete subpopulation of neurons situated in the zona incerta and LHA. In *ob/ob* leptin-deficient mice, MCH mRNA levels are increased and the administration of leptin reduces MCH expression [49]. Infusion of MCH in rats induces a significant hyperphagia with increase in body weight [49]. MCH knock-out mice are resistant to diet-induced obesity, due to increased energy expenditure and locomotor activity [62]. Several MCHR1 antagonists are under investigation as anti-obesity drugs (Table 2). Among these compounds, SNAP-7941 has proved able, in rats, to reduce food intake counteracting the effects of central MCH administration, and, given chronically, to decrease palatable food consumption and body weight.

Orexins (hypocretins)

The orexins (orexin A, OXA, and orexin B), two peptides derived from the common precursor prepro-orexin, were identified in 1998 [63]. They activate two closely related G protein-coupled receptors known as OX_1 and OX_2 . OXA, which appears to exert a more prominent orexigenic effect compared with orexin B, is expressed in neurons of the PFA, LHA and dorsomedial nucleus, with projections to neighboring hypothalamic nuclei and extra-hypothalamic areas including NTS [64].

A single intracerebroventricular injection of OXA increased feeding when administered during the light phase but not at the beginning of the dark phase, indicating that sensitivity to orexins might be subjected to circadian variations. Similarly, chronic administration of OXA over 8 days in rats increased food intake during daytime but caused a compensatory reduction of nighttime feeding, leaving daily food intake and body weight unchanged [64]. Studies on the potential use of OXA antagonists to reduce appetite in obese patients are in progress. Central administration of an antagonist to rats decreased feeding and accelerated the attainment of satiety and resting [65], while peripheral injection of OXA in humans did not affect eating behavior, though it reduced leptin levels and slowed gastric emptying [66].

Ciliary neurotrophic factor (CNTF)

CNTF, a member of the cytokine family including interleukin-6 and leukemia inhibitory factor, is a neuroprotective factor expressed in several motor neuron populations [67]. In a study evaluating the therapeutic potential of CNTF in amyotrophic lateral sclerosis, its administration induced a significant and sustained weight loss [68]. CNTF may exert the anorexigenic effect suppressing, in a leptin-like fashion, NPY expression in hypothalamus [67]. Indeed, CNTF administration inhibits the expression and release of both NPY and leptin in rats, indicating that the CNTF-induced inhibition of NPY is not mediated by leptin [67].

Of note, CNTF action on weight is long-lasting and no rebound weight gain is observed after cessation of treatment [69]. This is attributed to its ability to induce the growth of new leptin-responsive neurons [70].

In a 12-week randomized controlled trial involving 123 obese patients, daily subcutaneous injection of recombinant human variant CNTF (rhvCNTF) in association with hypocaloric diet was followed by a weight loss significantly higher than that observed in the control group (Table 2), but was accompanied by nausea, vomiting and cough, and associated with the appearance of anti-rhvCNTF antibodies [71].

Hypothalamic releasing hormones

CRH is highly expressed in PVN neurons and, when centrally injected, inhibits food intake and reduces body weight in rats [37]. Peripheral administration of human CRH increases energy expenditure and fat oxidation in humans [72]. Leptin infusion stimulates CRH expression, while pretreatment with a CRH antagonist attenuates the leptin-induced reduction of food intake and body weight [73]. In anorexia nervosa the ACTH response to CRH is inhibited, a finding compatible with enhanced spontaneous CRH secretion. The question as to whether this pattern may be, at least in part, responsible for the chronic blunting of feeding and the typical "drive for action" observed in this disorder is intriguing and still under debate [74].

Central injection of TRH reduces food intake and drinking in rats [37], and promotes a negative energy balance [75]. TRH expression in PVN is elicited by α -MSH, and inhibited by NPY and AGRP, both of which are likely to participate in the development of the central hypothyroidism occurring in rodents during fasting [76]. In rodents, leptin

enhances TRH secretion, while TRH inhibits leptin release. Interestingly, as TRH hyperactivity has been found to be correlated with hypertension in rats, it has been suggested that the link between obesity and elevated blood pressure could be represented, at least in part, by the leptin-TRH pathway [77].

GHRH effects on eating behavior are dose-dependently modulated. High doses inhibit feeding, while lower doses increase protein consumption in animal models [37]. In eating disorders such as obesity and anorexia nervosa, GHRH secretion is presumably reduced and enhanced, respectively, as suggested by the correspondent low and high serum GH levels recorded in the two disorders [78]. In the past, GHRH administration was reported to increase and reduce food intake in anorectic and bulimic patients, respectively, suggesting a possible role of GHRH in these abnormalities of eating behavior [78].

The endogenous cannabinoids

In the regulation of eating behavior, endogenous cannabinoids are emerging as important “carriers” of metabolic information from the central nervous system to the periphery and vice versa.

The orexigenic effect of exogenous cannabinoids, exerted through G-protein-coupled cannabinoid (CB) type 1 and type 2 receptors, is well known. The two principal endocannabinoids in the brain are anandamide (AEA), derived from membrane phospholipids, and 2-arachidonoylglycerol (2-AG), derived from triglycerides. They act as retrograde messengers, being secreted by postsynaptic cells and binding receptors on nerve terminals to inhibit synaptic transmission in either excitatory glutamatergic or inhibitory GABAergic axons [79]. Cannabinoids are also an important player in the reward circuitries, since they interact with opioid and dopaminergic systems to enhance satisfaction coming from the ingestion of palatable food [80].

Ob/ob leptin-deficient mice display elevated levels of hypothalamic endocannabinoids, which are reduced by leptin administration, an effect also documented in normal mice [83]. Circulating levels of endogenous cannabinoids are also increased in obese women compared with lean controls [81].

Confirming previous reports showing weight loss and improvement of metabolic features in obese animals treated with endocannabinoid antagonists [82], the recently published RIO (Rimonabant In Obesity) study demonstrated the efficacy of the

CB1 blocker SR141716 (rimonabant), given at the dose of 20 mg daily in addition to hypocaloric diet, in the treatment of human obesity [83] (Table 2). This antagonist was able to induce a decrease in body weight by 5% in 67% of the patients and by 10% or more in 39% of the cases, together with a significant reduction of waist circumference. Additionally, the drug significantly decreased the prevalence of dyslipidemia and metabolic syndrome. Owing to the interactions of endogenous cannabinoids with a number of supra-hypothalamic, hypothalamic and peripheral signals, the use of rimonabant, at the moment the most promising anti-obesity agent, may be accompanied by mood disturbances, especially depression, and gastrointestinal dysfunctions [83].

Monoaminergic neurotransmitters

Monoaminergic neurotransmitters interact with neuropeptides and hormones to control satiety mechanisms and eating behavior. Serotonin, produced in the dorsal raphe nucleus, reduces food intake and body weight by diminishing appetite and increasing energy expenditure [9]. Based on these properties several antiobesity agents have been developed, as the serotonin agonists fenfluramine and dexfenfluramine and the inhibitors of serotonin reuptake fluoxetine and sertraline (Table 2). However, fenfluramine and dexfenfluramine have been withdrawn from the market for serious adverse cardiovascular effects. Sibutramine, which is a combined serotonin and norepinephrine (NE) reuptake inhibitor, has proved efficacious in human obesity, causing a weight loss of 15% after 1 year of treatment. The drug is contraindicated in non adequately controlled arterial hypertension and in psychiatric disorders [84].

NE, synthesized in the dorsal vagal complex and the locus coeruleus, stimulates food intake through the activation of the α_2 -receptor, whereas stimulation of α_1 -, β_2 - and β_3 -receptors has the opposite effect [48]. In ob/ob leptin-deficient mice circulating levels of NE are elevated, suggesting a modulation of NE release by leptin as one of the mechanisms of action of the adiposity signal [9].

The effects of dopamine (DA) on food intake depend on the numerous receptor subtypes and brain sites of action. Indeed, DA signaling appears to suppress food intake in ARC and LHA, and to stimulate it in VMH [48]. Furthermore, mesolimbic pathways seem to be associated with the “rewarding” effects of palatable food through the activation of the D5 subtype receptor [85]. Repeated systemic treatment with D1, D2 or D1/D2 receptor

agonists reduces food intake. In ob/ob mice, leptin deficiency is accompanied by reduced DA levels, but the observation that incubation of rat hypothalamic extracts with leptin leads to the inhibition of DA release contrasts with the hypothesis of a direct correlation between leptin and the DA system [86] (Table 2).

Conclusions

The concepts on brain sites and mechanisms involved in the regulation of food consumption have evolved remarkably in the recent past, and new pathways have been added to the already complex network of central and peripheral messages controlling eating behavior and nutritional status. Satiety signals such as CCK, GLP-1 and PYY are delivered by the GI tract in concomitance to the meal and reach the brain chiefly through the vagus nerve. They are integrated with the adiposity signals leptin and insulin, and with additional central inputs, into the hypothalamic ARC, where a complex response modulating food intake is finally elaborated.

Some central signals, including NPY, AGRP, orexins and MCH, exert an orexigenic action, whereas others, such as POMC, CART, CRH and TRH, are anorexigenic. They are activated or inhibited according to the energetic balance of body, thus contributing to trigger anabolic or catabolic responses.

Thanks to its redundancy, this network can promptly compensate for any variation in its individual components. While this guarantees the nutritional homeostasis, it may thwart pharmacological interventions. The progressive elucidation of these mechanisms also allows the development of ever more specific molecules that reduce food intake and increase energy expenditure, thereby enhancing the catabolic pathways. Further, new types of genetic obesity are being recognized and this allows a more precise categorization of obese patients and a tailored pharmacological approach. On balance, the growing knowledge on the neuroendocrine control of food intake will lead to an ever greater choice of drugs for the treatment of obesity.

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