Neuroendocrine Mediators, Food Intake and Obesity: A Narrative Review.

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Abstract: Obesity is a chronic multifactorial disease caused by imbalance between caloric intake and energy expenditure. The Neuroendocrine system is one of the main factors regulating energy intake in humans. The Neuroendocrine system is made up of cells able to synthesize and secrete amines, peptides, growth factors and biological mediators, known as neurohormones, which modulate various biological functions by interacting with the nervous and immune system. In the central nervous system, neurosecretory elements are mainly located in the hypothalamus which is the anatomical site of the hunger (lateral nucleus) and satiety (ventromedial nucleus) centers; thus it plays a key role in chemical coding of food intake. Dopamine, Noradrenaline and Serotonin are historically considered key points in the regulation of feeding behavior. However, other neurohormones have been identified; these substances, also synthesized in peripheral tissues (especially adipose tissue and digestive tract), influence food intake. Some of these hormones have orexigenic activity; conversely, other substances have anorexigenic activity. A constant balance between orexigenic and anorexigenic neurohormones is essential to ensure a smooth feeding behavior, whereas a subtle and progressive disruption of neurochemical transmission is sufficient to induce hyperphagia or anorexia. Several factors affect the synthesis and release of neuropeptides: genetic, hormonal, psychological, environmental, receptorial, type of feeding and meal frequency. In the recent past some drugs, as Sibutramine and Rimonabant, modulating the activity of several neuroendocrine mediators (Serotonin, Noradrenaline, Endocannabinoids), have proven to be effective in reducing weight excess, even if they were withdrawn because of serious side effects. Recently, promising results in this way have been obtained with Glucagon like Peptide-1 analogs, showing significant efficacy in counteracting weight excess without side effects. Further knowledge developments on these complex neuroendocrine circuits and their hypothalamic interactions in food intake regulation could open new frontiers for effective pharmacological therapeutic approach to Obesity and other nutritional disorders.

Keywords: Food intake, Neuroendocrine mediators, Obesity.

INTRODUCTION

Obesity is a multifactorial chronic disease which reduces life expectancy and greatly increases health care spending, as it constitutes a serious cardiovascular risk factor by increasing morbidity and mortality [1, 2]. Obesity results from a prolonged imbalance between caloric intake and energy expenditure; so that body fat mass increases if a deregulation of energy balance occurs [2]. Appetite and energy balance are regulated by several neurochemical circuits and the Neuroendocrine system (NES) is one of the main factors which regulates caloric intake in humans. NES is made up of cells which synthesize and secrete amines, peptides, growth factors and biological mediators, so called neurohormones, which modulate various biological functions by interacting with the nervous and immune system. In the central nervous system (CNS), neurosecretory elements are mainly located in the hypothalamus, which is the anatomical site of the hunger and satiety centers located in the lateral area (LHA) and in ventromedial nucleus (VMN), respectively; thus the hypothalamus plays a key role in chemical coding of food intake.

Most studies about the role of neuromediators in the control of food intake were carried out at the end of the last century; these studies have allowed to shed light on many pathogenetic aspects of Obesity and have provided data for developing potential drug treatments. In the CNS Dopamine (DA), Noradrenaline (NA) and Serotonin (5-HT) are historically considered key points in the regulation of feeding behavior. However, in the last years many other neurohormones were identified; these substances, also synthesized in peripheral tissues, influence food intake and energy balance [3]. Some of these substances have orexigenic activity; conversely, other substances have anorexigenic activity. Adipose tissue, gastrointestinal tract, and pancreas are the main sources of these peripheral signals. The peripheral control of food intake includes afferent vagal nerves activated by distension of the gastrointestinal tract and by various gut hormones stimulating or inhibiting food intake. In the brainstem, the Nucleus of tractus solitarius (NTS) receives

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viscerosensory information and it serves as gateway for neural signals from the gastrointestinal tract to the hypothalamic centers [4]. The adipose tissue, the largest energy storage compartment, in the recent past has acquired the dignity of endocrine organ, because it was discovered to synthesize and release molecules, known as adipokines, which play endocrine, autocrine or paracrine roles [5].

A constant balance between orexigenic and anorexigenic neurohormones is essential to ensure a smooth feeding behavior, whereas a subtle and progressive disruption of neurochemical transmission is sufficient to induce hyperphagia or anorexia. Several factors influence the synthesis and release of neuropeptides: genetic, hormonal, psychological, environmental, receptorial, type of feeding and meal frequency. [3]

This work reviews the most insights about the complex and redundant molecular mechanisms which regulate food intake, focusing on the most encouraging perspectives for the treatment of obesity.

HYPOTHALAMIC NEUROHORMONES MODULATING FOOD INTAKE

Several studies have identified in the hypothalamus neuronal sites responsible for the synthesis and release of orexigenic and anorexigenic neurotransmitters and their receptors. These hypothalamic neurons are able to produce more neurotransmitters and they are connected by a wide network of neuronal pathways. This intricate brain network integrates and releases orexigenic and anorexigenic signals, resulting in a complex circuit, the Appetite Regulation Network, which adjusts eating behavior [6-8]. In addition to the VMN, site of the satiety center, and in addition to the LHA, the integration center for olfactory, visual, digestive and metabolic information promoting food intake, other hypothalamic areas, such as the paraventricular nucleus (PVN), dorsomedial nucleus (DMN) and arcuate nucleus (ARC) are charged of monitoring food intake. Historically, classical neurotransmitters which play a role in modulating eating behavior and energy homeostasis are Dopamine (DA), Noradrenaline (NA) and Serotonin (5-HT) [9].

Several evidences have confirmed that DA release in specific hypothalamic regions, such as the LHA, encourages food intake [10-12]. In contrast, several experimental studies have shown the anorexigenic activity of 5-HT; this effect is mediated by serotonin receptors located in the VMN and it appears to be selective for carbohydrate-containing foods. Moreover, 5-HT would responsible for reducing the amount and frequency of food eaten [13, 14]. The noradrenergic system is involved in the appetite regulation through a dual mechanism: the activation of α1-receptors inhibits food intake while the activation of presynaptic α2-receptors causes opposite effect on nutrition [15]. A significant number of α1- and α2-adrenergic receptors were observed in the PVN and several experimental studies have shown that the two classes of receptors often act in antagonism [16,17]: NA release from presynaptic terminals stimulates food intake probably by activation of α2-receptors [18] while α1-receptor stimulation by agonists, such as Phenylpropanolamine and Amifedrina, causes a dose-dependent inhibition of food search; this effect is totally blocked by pretreatment with a1-receptor antagonists, such as Prazosin and Benoxathian [19]. In addition, it has been shown that activation of α1-adrenergic receptors in the VMN generates postsynaptic excitatory potentials while α2-receptor stimulation produces inhibitory potentials. It's very likely that, at baseline, the anorexigenic effect of NA mediated by α1-receptors may be predominant [16, 20, 21].

Based on this knowledge, Researchers have directed their efforts towards the synthesis of drugs able to counteract body weight gain by reducing food intake. In the past years, many medications able to reduce appetite and food intake, by acting on noradrenergic and serotoninergic systems, have been introduced and approved by the United States Food and Drug Administration. However, most of them such as Phentermine [22], Fenfluramine and its d-isomer Dexfenfluramine [23], were subsequently withdrawn due to serious cardiovascular adverse effects. Most recently, Sibutramine, an inhibitor of serotonin and norepinephrine reuptake [24], was withdrawn on the same grounds.

There are several evidences supporting the role of brain Histamine in food intake regulation. Histamine neurons, localized in the hypothalamic tuberomammillary nucleus (TMN), project to numerous brain regions. Histamine is a neurotransmitter able to inhibit appetite by interacting with H1- and H3-receptors in the VMN and PVN [25-29]. Some studies in rats have shown that treatments increasing the availability of brain Histamine, or drugs which activate H1-receptors in the CNS, suppress food intake [30-32]; conversely, the treatment with H1-receptor antagonists

or the administration of Histidine decarboxylase inhibitors which decreases the brain levels of Histamine, increase food consumption and body weight [27, 33]. Experimental observations in rodents seem to agree that H3-receptors blockade in the hypothalamus is beneficial for decreasing food intake and body weight [34,35], whereas H3-receptor agonists enhance feeding in rats [36]. H3-receptor antagonists increase Histamine release from the hypothalamus [37] because H3-receptors are presynaptic autoreceptors which inhibit Histamine synthesis and release; moreover, they also inhibit other neurotransmitters which control food intake, such as 5-HT, DA and NA.

More recently, many other neurohormones synthesized in the CNS and able to influence food intake, have been identified; of these, Neuropeptide Y (NPY) and α -Melanocyte Stimulating Hormone (α-MSH) seem to be more involved in appetite control.

Orexigenic signals

NPY is widespread within the CNS, where it plays important effects on appetite stimulation, water intake and mood. NPY-producing neurons are located in different brain areas; in particular, food intake would be controlled by two neuronal subpopulations: the nerve cells of the brainstem and the hypothalamic neurons of the ARC which project afferents to the DMN, PVN and LHA [8, 38]. NPY represents the best known orexigenic agent: the administration of this peptide in different hypothalamic areas [39] and in the fourth cerebral ventricle causes a strong appetite stimulation [40] and reduces the energy consumption [41]; furthermore, chronic administrations of NPY cause hyperphagia and obesity [42,43]. The orexigenic action of NPY seems linked to the activation of two receptor subtypes, Y1 and Y5 [44]. NPY synthesis and release have a circadian pattern [45] and NPY release is influenced by 5-HT which seems to play an inhibitory role on NPY [9,46]. Moreover, gonadal hormones, glucocorticoids, insulin and some cytokines have modulatory effects on NPY synthesis and release [47-50].

In several studies, a 19-amino acids cyclic neuropeptide, the Melanin-Concentrating Hormone (MCH), has proven potential orexigenic effects, less mighty and prolonged than NPY [51,52]. However, there are contrasting data about the involvement of this hypothalamic neuropeptide in the appetite regulation [53], although the evidences on its orexigenic effect [54, 55] seem to prevail on its anorexigenic activity [56, 57].

Two other appetite-stimulating neuropeptides, Orexin-A and Orexin-B, are synthesized in the LHA neurons and act on two receptors, OXR1 and OXR2. Orexin-producing neurons project to NPY-containing neurons in the ARC; NPY neurons express OXR1-receptors and receive excitatory signals. Orexins have lower orexigenic effects than NPY and their activity may be due, at least in part, to stimulation of NPY neurons [58, 59]. Orexin-containing neurones intermingle partially with histaminergic neurons in the posterior hypothalamus. Orexin-A perfusion into rat stimulates food intake [60] and this effect seems to involve pathways mediated by Histamine H1-receptors. Finally, in vitro studies have shown that Orexins inhibit 5-HT release in the hypothalamus [61].

According to some evidence, endogenous Cannabinoids such as Anandamide and 2-arachidonoyl-glycerol (2-AG), by interacting with their type-1 receptor (CB1), facilitate food intake and reduce energy expenditure [62]. Moreover, in mice (CB1 -/-) with a disrupted CB1 gene [63, 64] and in rodents treated with CB1 antagonists, the lack of CB1-receptors induces anorexigenic effects [65]. CB1-receptors are widely distributed in the hypothalamus and the Endocannabinoid system seems to affect the secretion of other peptides involved in feeding behavior [66, 67]. In particular, an interaction between Endocannabinoid system and NPY has been shown in rats: two CB1 agonists, CP55, 940 and Anandamide, are able to significantly increase NPY release in the hypothalamus [68]. In the recent past, the CB1 antagonist Rimonabant has been used for drug therapy of obesity; unfortunately, few years later it was withdrawn due to uncontrollable psychiatric adverse effects. [69].

Anorexigenic Signals

The orexigenic action of NPY is counteracted by the anorexigenic effect of α-MSH, also known as α-Melanocortin, a peptide widely distributed in the hypothalamus which derives from Proopiomelanocortin (POMC), a 267-amino acids polypeptide hormone precursor [70]. Five α-MSH receptor subtypes have been identified and only two receptors, MC3 and MC4, are also expressed in the hypothalamus: MC3-receptors are located in the limbic system and ARC, whereas MC4-receptors are spread throughout hypothalamus, predominantly in the PVN and LHA [71]. The activation of POMC neurons, which express insulin and serotonin receptors, promotes α-MSH secretion [72]. In addition, POMC neurons interact with NPY

system: in the ARC, axons responsible for NPY release project toward POMC neurons, inhibiting their activity by γ-aminobutyric acid (GABA) release, the main inhibitory neurotransmitter of the CNS [73]. The dualism between these neuropeptidic systems is also expressed by complete suppression of NPY orexigenic effect after administration of α-MSH agonists [73].

A protein able to influence the anorexigenic activity of α-MSH is the Agouti protein, primarily identified in the Agouti lethal yellow (Ay/a), a murine strain which represents a model of genetically determined obesity [74]. Agouti Signaling Protein (ASP), expression of gene mutation, acts as an antagonist of MC4-receptor by increasing food intake and body weight; moreover this protein induces chronic hyperglycemia [75]. Recently, a new gene, the Agouti Related Transcript (ART), has been identified in the hypothalamus; it presents high homology to Agouti gene and encodes for a protein Agouti related, the Agouti Related Peptide (AgRP). AgRP is a potent and selective antagonist of MC3 and MC4 receptors [76,77] and evidences that neurons located in the ARC, where NPY and ART/AgRP are co-expressed [78], as well as evidences that NPY and AgRP are co-released in the PVN, suggest that AgRP may help to block the anorexigenic effect of α –MSH [9].

In addition to α-MSH, POMC also generates ß-endorphin, an opioid peptide released from the ARC neurons projecting in the VMN, DMN and PVN [79,80]. Microinjections of ß-endorphin stimulate food intake by activation of μ-opioid receptors [6, 8, 81]. Other opioid peptides, such as Dynorphin A, Methionine-Enkephalin and Leucine-Enkephalin, widely secreted in the hypothalamus, induce food intake by activation of κ- and δ-receptors [6, 82-84]. The orexigenic effect of endogenous opioids is less sustained and pronounced than NPY activity [83]; anatomical studies have shown the existence of synapses between axon terminals of NPY neurons and dendrites and soma of ß-endorphin neurons. Therefore, it has been hypothesized that NPY could increase food intake directly, or by favoring ß-endorphin release [85].

Another neuropeptide strictly related to the melanocortin system for the purposes of anorexigenic effect is the Cocaine - and Amphetamine-Regulated Transcript (CART). This peptide originally takes name from the isolation of messenger RNA produced by striatal neurons of rats, after treatment with psychostimulant drugs, such as Cocaine and Amphetamine [86,]. Later studies have shown the fragmentation of CART in several shorter peptides in the hypothalamic-pituitary axis and in the adrenal gland. These findings lead to the hypothesis that CART fragments play various biological functions in the nervous and endocrine system [86, 87]. CART-producing neurons were found in the hypothalamus and limbic system; in particular in the ARC, CART neurons also express POMC [88]. CART peptide is an important anorexigenic signal: the intraventricular administration of this neuropeptide inhibits food intake; moreover, CART completely blocks the anorexigenic effect of NPY [9, 88, 89].

Corticotropin-Releasing Hormone (CRH) also exerts inhibitory effect on food intake [6,90,91]; this neuropeptide secreted by hypothalamic neurons in the pituitary portal circulation is known to stimulate the release of Adrenocorticotropin hormone (ACTH) from the adenohypophysis [92]. CRH-producing neurons are mainly located in the PVN and they project up to the extreme zone of the median area [93]. CRH release is regulated by a circadian rhythm linked to the sleep-wake cycle and its secretory spikes are in response to particular stress [94]. CRH microinjections in different hypothalamic areas have identified the sites responsible for anorexigenic action of CRH, probably mediated by two receptor subtypes, CRH-R1 and CRH-R2 [95]. CRH neurons interact with other neuronal systems involved in the appetite regulation; in fact, these neurons express Y5- and MC4-R-receptors in the hypothalamus [96, 97]. Therefore, it was suggested a link between CRH, NPY and melanocortin system: CRH acts in the PVN by inhibiting the orexigenic action of NPY [95]; conversely, CRH production is stimulated by central administration of melanocortin agonists, while the antagonists inhibit this effect. Some studies have found other peptides produced by hypothalamic neurons such as Urocortine, belonging to the same family of CRH and with a primary structure partly homologous [98]; this peptide has a high binding affinity for CHR-R1- and CHR-R2-receptors [99].

PERIPHERAL OREXIGENIC NEUROHORMONES

Several neurohormones, synthesized in the peripheral tissues, particularly in the adipose tissue and digestive tract, influence food intake; some of these substances have orexigenic activity. Ghrelin is a 28-amino acids polypeptide which exerts a strong effect on growth hormone (GH) release by acting directly on the pituitary gland. Although Ghrelin is more expressed in the stomach, it is also produced in the pancreas, kidney, immune cells, pituitary gland and ARC [100-

104]. In the CNS Ghrelin receptors are expressed in the hippocampus and pituitary gland: this distribution suggests a possible role of Ghrelin in the hypothalamic mechanisms of appetite regulation [104]. It was shown that Ghrelin, when centrally administered, exerts a potent orexigenic effect slightly lower than NPY [105]. An important role in the modulation of Ghrelin orexigenic effect seems to be done by NPY and AgRP, since their messenger RNAs are overexpressed in the hypothalamus after chronic treatment with Ghrelin [106,107]. The simultaneous administration, at Y1-receptor, of NPY antagonists and Ghrelin reduces the orexigenic effect of the hormone: these experimental evidences confirm the correlation between NPY and Ghrelin [103,108]. In turn, Ghrelin inhibits melanocortinic fibers probably by stimulating neurons of NPY/AgRP system [109]. In addition, there is evidence of a functional correlation between Ghrelin and Endocannabinoid system: Rimonabant, a CB1-receptor antagonist, in the hypothalamus is able to inhibit the orexigenic response Ghrelin administration [67]; thus the orexigenic effect of Ghrelin could be mediated by endocannabinoid release in the PVN.

Galanin (GAL) is a 29-amino acid peptide isolated in the small intestine and diffusely distributed in several sites, including the PVN, VMN and LHA [110]; intraventricular or hypothalamic injections of GAL stimulate food intake in rats already satiated [111-113]. There is a close anatomical and functional correlation between GAL-synthesizing neurons and other orexigenic signals in the brain of rats; in particular, neurons which produce NPY are in direct communication with those involved in GAL synthesis, especially in the ARC and PVN [114]: therefore we can hypothesize a synergistic effect of both peptides in the modulation of feeding behavior [8]. However, as demonstrated in several studies, the orexigenic effect of GAL is lower and shorter (30 minutes) compared to NPY. In addition, GAL-synthesizing neurons establish synaptic connections with ß-endorphin axon terminals in the ARC, so as to increase ß-endorfine release; on the other hand, pretreatment of rats with Naloxone, an opioid receptor antagonist, reduces GAL-induced food intake [111].

Peptide YY (PYY) is a gut hormone, belonging to the pancreatic polypeptides family, present in bloodstream in two main forms: PYY (1-36) and PYY (3-36) [115, 116]. PYY (1-36) is released after meal from intestinal L cells and exerts several gastrointestinal functions: it inhibits gastric acid secretion, pancreatic exocrine secretion and gastrointestinal motility; moreover it reduces mesenteric circulation [117-121]. Some studies have shown that PYY (1-36), although in low concentrations, is present in the CNS of mammals and it is able to cross the blood/brain barrier [117-119]. In particular, PYY (1-36)-containing neurons are located in hypothalamic areas and hindbrain [120] while its receptors are thickly distributed in the limbic system and thalamic nuclei [121-123]. This peptide has high structural homologies with NPY and several studies confirm that the orexigenic effect of PYY (1-36) is greater than NPY [124]. Although both peptides implement their hyperphagic effects by binding to specific receptor subtypes (Y1 and Y5) with comparable affinity, the difference probably is a longer link between receptors and PYY (1-36); this prolonged interaction may explain its higher orexigenic action than NPY [122, 125]. It is likely that PYY (1-36) expresses orexigenic effect by activation of different nutritional and motivational factors. Some studies [39,126] confirm that PYY (1-36) stimulates appetite; it also increases the hedonic value of food and influences dietary habits by changing the way to get food. Clinical trials have also shown some relationship between bulimic behavior and PYY (1-36) [127,128]. The involvement of the serotoninergic, adrenergic and opioidergic systems [129-131] in PYY (1-36)-induced hyperfagic behavior is widely recognized, but limited data are currently available about a possible involvement of the histaminergic system. However it has been demonstrated [132] that intraventricular infusion of the H3-receptor antagonist Tioperamide causes a dose-dependent decrease of hyperfagic effects induced by PYY (1-36). Since H3-receptors are also involved in the release of other neurotransmitters as NA, DA and 5-HT, it is possible that Tioperamide reduces the orexigenic effect of PYY (1-36) by modulating the release of other monoamines involved in appetite regulation. Pharmacological targeting of the PYY system could represent a promising strategy to treat obesity in the next future.

PERIPHERAL ANOREXIGENIC NEUROHORMONES

The main signal originating from the adipose tissue is Leptin, which promotes the activation of anorexigenic pathways in the CNS; furthermore, Leptin stimulates the adrenergic system, so as to increase the energy expenditure. Leptin is a 167-amino acids hormone, encoded by ob gene, which is secreted from the adipocytes in amounts proportional to their number and size [133, 134]. Leptin is able to cross the blood/brain barrier and reaches the CNS via a saturable transport

system located in the endothelial cells [135]. The pulsating production of Leptin occurs according to a circadian rhythm, with lower concentrations in the morning, progressively increasing up to achieve a night peak [136]. Membrane receptors for Leptin are located in the hypothalamic nuclei and exist in different isoforms; the most important are the short isoform (Ob-R), which is involved in the transport mechanisms of Leptin in the CNS, and the long isoform (Ob-Rb), responsible for the metabolic effects of Leptin and widely distributed in the hypothalamus [137-139]. In humans, in both normal weight and obese subjects, serum levels of this hormone are related to adipose mass and body weight; Leptin secretion undergoes a drastic drop in the fasting state and it is greatly stimulated in case of excessive caloric intake or increased body fat; indeed in obese patients circulating levels of Leptin are quite high [140-142]. Leptin is a key hormone for the maintenance of energy homeostasis and body weight, by which the hypothalamus detects the nutritional status of the organism [143]. Central and peripheral administration of Leptin reduces food intake and body weight in both normal and genetically obese mice (ob/ob), which are characterized by lack of this hormone. It seems that Leptin is not able to inhibit the spontaneous food intake, but rather to reduce the amount of food eaten during a single meal [144].

Several studies in animal models have revealed the occurrence of Leptin resistance in genetically obese Zucker rats (fa/fa) and in both diabetic (db/db) and agouti (AY/a) mice, as well as in mice lacking MC4-receptors and in those taking high-fat foods; in these rodents Leptin hypersecretion was observed [145-149]. In many obese patients have been observed a loss of Leptin-induced anorexigenic effects, probably due to alteration of transport mechanisms of this peptide across the blood/brain barrier [150], or resulting from structural aberrations of Ob-Rb receptor, or secondary to changes in the mechanism of post-receptorial signal transduction [9, 51].

Leptin interacts with many other peptide systems involved in the hypothalamic regulation of appetite. In this regard, a large number of experimental evidences suggests an interaction between Leptin and NPY: Ob-Rb and NPY receptors are co-expressed in the ARC [152]; in both normal and genetically obese (ob/ob) mice, subjected to fasting conditions, NPY gene expression is inhibited by Leptin in the ARC [153,154]; Leptin reduces NPY levels in the hypothalamic nuclei [154] and inhibits NPY-induced food intake [153].

It has been observed that Leptin significantly reduces GAL and MCH gene expression; after weight loss there is a reduction of circulating Leptin levels and both appetite-stimulating and energy expenditure-reducing responses are activated, probably by increasing NPY, GAL and MCH gene expression [154]. The localization of Ob-Rb receptors in neurons which produce MCH and GAL suggests that these neuropeptides can modulate the anorexigenic effects of Leptin [155]. Leptin receptors were also identified in Orexin-producing neurons, whereby it is possible that Orexins can also mediate Leptin activity [58].

On the contrary, during weight gain has been observed an increase in blood Leptin levels with over expression of POMC [156] and CRH [154] in the PVN, resulting in food intake reduction. The expression of Leptin receptors in POMC neurons suggests that Leptin stimulates α-MSH production [157]. The direct correlation between CRH and Leptin is confirmed by the observation that CRH antagonists inhibit the anorexigenic effect of the hormone; instead, central injections of Leptin increase CRH-mRNA synthesis and CRH-R2 gene expression [158].

The monoaminergic system could also be involved in the mechanisms which modulate Leptin activity; indeed this hormone inhibits DA and NA release from hypotalamic synaptosomes in rats [159]; moreover, the lack of DA, observed in case of hyperphagia secondary to Leptin deficiency, suggests a potential modulating action of this catecholamine on Leptin effects [10]. A possible role of Leptin in the modulation of 5-HT activity has also been evaluated: peripheral or intracerebroventricular administration of adipose-tissue hormone appears to stimulate the serotoninergic turnover in mice [160] while, in the frontal cortex, the serotoninergic transporters decrease after intracerebroventricular administration of Leptin [161].

Leptin could affect the feeding behavior by activating Histamine-containing neurons; indeed, administration of Histidine decarboxylase inhibitors to rats decreases Leptin-induced suppression of food intake, so as Leptin-induced hypophagia is diminished in H1 receptor-deficient mice [162].

Finally, Leptin reduces the hypothalamic levels of Anandamide while the concentrations of Anandamide and 2-AG are increased in db/db mice or in fa/fa Zucker rats which have Leptin resistance [163]; therefore hypothalamic Endocannabinoids could be under inhibitory control of Leptin.

Insulin, the first hormone historically involved in the appetite control, is required to determine Leptin secretion by adipocytes; moreover the central action of Insulin reduces food intake and stimulates catabolic pathways, by inhibiting AgRP/NPY neurons and stimulating POMC/CART neurons [164].

Pancreatic ß-cells, in addition to insulin, also secrete Amylin, a 37-amino acids polypeptide which is stored in granules and secreted with insulin after nutrients intake or in response to hyperglycemia [165-167]. Amylin influences glucose homeostasis by inhibiting glucagon secretion and modulating gastric emptying and insulin secretion [168]. Plasma Amylin levels increase in obese patients and in subjects with insulin hypersecretion [169]; conversely, hormone levels are low in type 1 diabetes mellitus [166]. Amylin exerts anorexigenic effect [170] after peripheral [171] or central [165] administration and crosses the blood/brain barrier; in the CNS it shows high affinity with different binding sites [172, 173]. It is not clear how Amylin plays a role in food intake inhibition: intraperitoneal administration of Amylin induces anorexigenic effects by dopamine D2-receptors [174] and it has been shown that Amylin inhibits DA release from hypothalamic synaptosomes [175]; in addition, chronic administration of Amylin leads to decreased NPY levels and increased CCK concentrations in the CNS [176, 177].

Glucagon like Peptide-1 (GLP-1) is another important hormone which plays a key role in modulating food intake; it is a potent inducer of glucose-dependent insulin secretion and is mainly synthesized in the intestinal L cells [178]. As other gastrointestinal peptides, GLP-1 is also localized in the CNS; in particular, GLP-1 is expressed in caudal neurons of the NTS which project to several hypothalamic areas, including the ARC and PVN [179]. Intraventricular administration of GLP-1 inhibits food intake in fasting rats and this effect is abolished by the concomitant administration of Exenedin (9-39) amide, a potent GLP-1 antagonist [180, 181]. The anorexigenic activity of GLP-1 could be mediated by NPY transmission; indeed, NPY-induced food intake is inhibited by GLP-1 and stimulated by Exenedin (9-39) [180, 182]. Some studies have shown that Leptin receptors and GLP-1 mRNA are co-expressed in the brainstem neurons and this observation suggests that GLP-1 may mediate the anorexigenic effects of Leptin [183, 184].

Histamine partially mediates the appetite suppression of GLP-1, because the anorexigenic effect is reduced by pharmacological or genetic loss of H1-receptor function [185]. GLP-1 synthesis is regulated not only by a combination of neuroendocrine stimulating factors, but also by direct contact of nutrients with enteroendocrine cells; after secretion, the hormone is rapidly degraded in bloodstream by the enzyme dipeptidyl peptidase IV (DPP-4) [186]. GLP-1 also reduces the pancreatic secretion of α-glucagon [186] and exerts extrapancreatic effects which are potentially relevant for therapeutic applications [187]; indeed, GLP-1 inhibits gastric emptying and gastric acid secretion [188, 189].The main limitation to the therapeutic use of GLP-1 is its short half-life that is less than two minutes; to overcome this drawback there are two approaches: 1) to make use of GLP-1 synthetic analogs, resistant to the action of DDP-4, so as to prolong their stimulating effect on GLP-1 receptors; 2) to utilize selective DPP-4 inhibitors, able to prevent the degradation of endogenous GLP-1 so as to increase its circulating levels [190]. In several studies two GLP-1 receptor agonists, Exenatide and Liraglutide, have shown to inhibit appetite and reduce food intake without affecting energy expenditure, obtaining weight loss in prolonged treatments [191]. This result seems particularly evident using GLP-1 analogs in combination with metformin, suggesting a possible positive interaction of drugs [192]. Open-label extensions of double-blind clinical trials show that the weight reduction proceeds, without plateau, up to three years of treatment [193]. Then, it seems that GLP-1 analogs, unlike other drugs which reduce body weight, do not induce tolerance to their weight effects, at least in medium term. Unlike GLP-1 analogs, DPP-4 inhibitors do not determine weight loss nor modify body weight [192]. These findings indicate that GLP-1 analogs might become an interesting therapeutic option in obese patients [191].

The enzyme DPP-4, acting on gastrointestinal peptide YY (1-36), produces the fragment (3-36) by loss of N-terminal dipeptide Tyr-Pro. The fragment (3-36) of the peptide YY, belonging to the pancreatic polypeptides family, has an high sequential homology with NPY and mediates its endogenous effects by a greater selectivity for Y2 inhibitory autoreceptors, widely expressed on NPY/AgRP neurons of the ARC [109,194,195]. Peptide YY and its fragment (3-36) have opposing effects in the regulation of feeding behavior; indeed, peptide YY (3-36) shows anorexigenic effects when it is released into the bloodstream in response to food intake. Plasma levels of Peptide YY (3-36), rather low before meals, grow up after food ingestion until

they reach a peak within 90 minutes and remain elevated for many hours. Since the peak plasma level is proportional to the caloric intake, this peptidic fragment is an important signal interconnecting gut and brain circuits which regulate food intake [195]. Peripheral infusions of this peptide induce a sensible appetite reduction in rats and humans; experimental studies on humans have shown that administration of peptide YY (3-36), in normal postprandial concentrations, significantly decreases appetite and reduces food intake at least 24 hours [194-196]. Therefore, chronic administration can lead to significant weight loss; thus peptide YY (3-36) could be a valuable therapeutic approach in the obesity treatment. Some studies have assessed whether obese individuals have, as to Leptin, a resistance to peptide YY (3-36): in contrast to Leptin, the results have not shown resistance to the anorexigenic effects of peptide YY (3-36) in obese subjects; on the contrary, the levels of this peptidic fragment were minimal and this result has suggested that the deficiency of this peptide may contribute to the pathogenesis of obesity [196]. Finally, studies in rats suggest that peptide YY (3-36) and Ghrelin act in opposition in food intake regulation by indicating "positive" and "negative" energy states, respectively. The opposing action Ghrelin-Peptide YY (3-36) seems to be at the root of the therapeutic success resulting from gastric and intestinal by-pass; indeed, patients undergoing this type of bariatric surgery, before the meals have a reduction in circulating Ghrelin levels and a significant increase in plasma levels of Peptide YY (3-36) [197-198]. This effect leads to a continuous reduction in the compulsive behavior toward food, with subsequent weight loss already detectable a few days after the surgery [199].

Oxyntomodulin (OXM) is another hormone released from enteroendocrine L-cells after digestion, which induces satiety by acting via GLP-1 receptors in the ARC. Circulating levels of OXM are elevated in several conditions associated with anorexia; central injections of OXM reduce food intake and body weight in rodents suggesting that OXM sends signals about food ingestion to the hypothalamic appetite-regulating circuits. OXM administration in animals and humans causes weight loss by reducing food intake in combination with increasing energy expenditure. Thus, the development of long-acting analogs of OXM is an exciting new therapeutic avenue for addressing the global obesity epidemic [200-202]

Recently, it has been demonstrated that Preproghrelin may undergo an additional proteolytic cleavage, generating a 23-amino acid peptide named Obestatin. Unlike Ghrelin, Obestatin has anorexigenic effects and reduces gastric emptying and jejunal contractions, counteracting weight gain; however, some studies have not reproduced these results [203,204]. It has been reported that Obestatin is unable to cross the blood–brain barrier and is rapidly degraded in bloodstream [205]. An alternative hypothesis is that Obestatin exerts its effects on eating through direct interactions with the gastrointestinal system, by suppressing the gastric emptying and reducing the contractile activity of muscle strips in jejunum. Thus, the inhibition of jejunal contraction could generate an afferent vagal signal to induce satiety in the brain. [206].

Finally, the brain-gut peptide Cholecystokinin (CCK) might play a role in the control of food intake. CCK is secreted from I-cells of the small intestine and acts as an endogenous signal of postprandial satiety. Peripheral administration of CCK reduces food intake in humans and animal models [207-209]. Feeding inhibitory actions of the hormone are mediated by interaction with CCK receptors expressed in the brainstem and hypothalamus [210]. It has also been reported that Ghrelin attenuates the effect of CCK on appetite while Leptin synergistically enhances CCK activity [211].

CONCLUSION

Food intake is regulated by a complex system of central and peripheral signals which interact in order to modulate the individual response to nutrients. The peripheral regulation includes signals generated in the adipose tissue and gastrointestinal tract while central control is implemented by neuroendocrine mediators in the hypothalamus, the integration center of several nutrient signals.

The main circulating signal originating from the adipose tissue is Leptin, which promotes the activation of anorexigenic pathways in the CNS. Gastrointestinal tract and pancreas also contribute with several circulating peptides, as Ghrelin, GAL, PYY, Insulin, Amylin, GLP-1, Oxyntomodulin and CCK that variously influence food intake by acting on hypothalamic neurons directly, after crossing the blood–brain barrier. Other gastrointestinal signals reach the NTS, in the caudal brainstem, through the vagus nerve. From NTS afferent fibers project to the ARC, where these afferences are integrated with adiposity signals and hypothalamic inputs, making a complex network of

neuroendocrine circuits which finally elaborate the individual response to meal.

The ARC contains two major populations of neurons controlling appetite with opposing effects on food intake: a subset of neurons co-expressing NPY and AgRP which increase food intake, and another subpopulation co-expressing POMC, α-MSH and CART which inhibit food intake. Axons of these neurons project to "second-order" neurons located in hypothalamic areas, downstream the ARC, also involved in the control of food intake: the PVN is the site where anorexigenic peptides, as CRH, are secreted while the LHA is the area where orexant molecules, as MCH, are produced.

The balance between the activities of these complex and integrated neuroendocrine circuits is critical to regulate food intake and control body weight.

In the past years, some drugs modulating the activity of several central neuroendocrine mediators have proven effective in reducing weight excess, even if they were withdrawn because of their serious adverse effects. Recently, promising results in this way have been obtained with analogs of a peripheral mediator, GLP-1, showing significant efficacy in counteracting weight excess without side effects.

The knowledge about NES is continuously evolving and, at the time, we probably can see just the tip of an iceberg. Better understanding of these systems could help to clarify uncertain pathogenetic aspects of the weight gain. Moreover, further knowledge development on these complex neuroendocrine circuits and their hypothalamic interactions in the regulation of food intake could open new frontiers for effective pharmacological therapeutic approaches to Obesity and other nutritional disorders.

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