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Endocrine, Metabolic & Immune Disorders-Drug Targets, **XXXX,** ***XX*****, 1-11**

REVIEW ARTICLE

Neuroendocrine Modulation of Food Intake and Eating Behavior

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Abstract: ***Background:*** In the first section of this review, we examined the neuroanatomical and neurochemical data on hunger and satiety centers, glucose receptors, sensorial influences on eating behavior, and regulation of energy requirements. The second section is devoted to orexigenic and anorexigenic hormones.

Objective: This paper aimed to overview and summarize data regarding the role of neuroendocrine regulation of food intake and eating behavior.

Methods: Appropriate keywords and MeSH terms were identified and searched in MEDLINE/PubMed. References of original articles and reviews were examined.

Discussion and conclusion: *Hunger and satiety center are located in the lateral (LH) and ventromedial hypothalamus (*VMH). Lasting aphagia has been observed following a lesion of LH, while hyperphagia is induced by LH stimulation. On the other hand, increased food intake after VMH lesion and aphagia following VMH stimulation in hungry animals has also been reported. Intracellular glucopenia triggers food intake by reducing neuronal activity at the satiety center level. Moreover, sensory influences are regulated by food palatability as the positive hedonic evaluation of food and energy requirement indicates the average amount of food energy needed to balance energy expenditure. Orexigenic and anorexigenic hormones secreted from the gastrointestinal tract and adipose tissue regulate brain areas involved in eating behavior *via* gastric afferent vagal nerve, circumventricular organ area postrema, or transporter system. Finally, oxytocin (OT) plays a role in reward-related eating by inhibiting sugar intake and decreasing palatable food intake by suppressing the reward circuitry in the brain. Moreover, the anorectic effect of nesfatin-1 is abolished by an OT antagonist.

ARTICLEHISTORY

Received: June 29, 2021
Revised: October 26, 2021
Accepted: December 24, 2021

DOI:
10.2174/1871530322666220127114326

Keywords: Eating behavior, ghrelin, cholecystokinin, glucagon-like-peptide-1, peptide YY, leptin, oxytocin, nesfatin-1 neuroendocrine modulation, food intake.

1. INTRODUCTION

Hypothalamic nuclei play an important role in regulating food intake and eating behavior. Notably, food intake is stimulated by neurons located within the lateral hypothalamus (LH), constituting the so-called "hunger center." On the other side, ventromedial hypothalamic nuclei (VMH) represent the so-called "satiety center" and suppress appetite. This paper discusses the roles of neuroanatomical areas in the neuroendocrine control of food intake and eating behavior [1, 2].

Several hormones regulating appetite and satiety, namely ghrelin, cholecystokinin (CCK), glucagon-like-peptide-1 (GLP-1), and peptide YY (PYY), are secreted by the gastrointestinal (GI) tract. Conversely, leptin is secreted by the adipose tissue [3]. In addition, the hypothalamic hormones oxytocin (OT) and nesfatin-1 could exert anorectic effects [4]. These peptides act in the brain *via* circumventricular organs (CVO), which lack the blood-brain barrier (BBB). The others act *via* vagal nerve afference and OT *via* efferent projections synapsing to brainstem nuclei or from dendrites of OT-ergic hypothalamic neurons (Fig. **1**).

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1389-2010/XX $65.00+.00

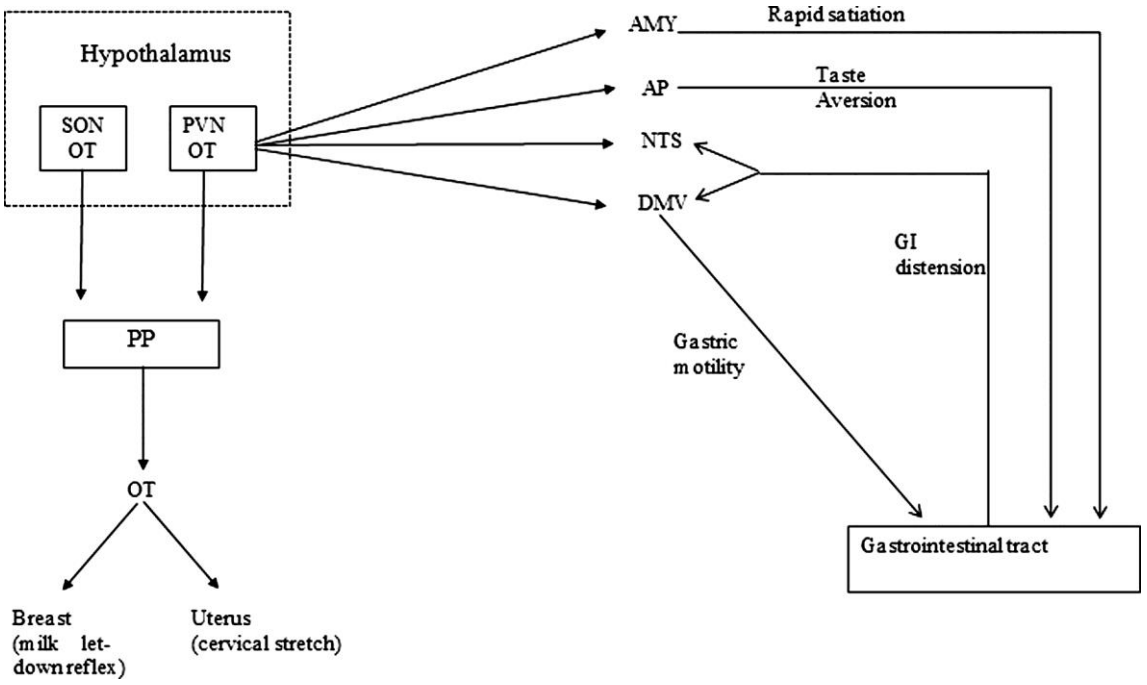

Fig. (1). Pathways of peripheral signals accessing to the brain from gastrointestinal hormones ghrelin, cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY (PYY), from adipose tissue leptin, and from hypothalamic paraventricular nuclei (PVN) oxytocin (OT) and nesfatin-1 (NF-1). (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).
Abbreviations: BBB: blood-brain-barrier; CVO AP: circumventricular organ area postrema; PP: posterior pituitary; ObRs: leptin receptors; NTS: nucleus of the solitary tract; VMH: nuclei of the ventromedial hypothalamus.

2. HUNGER AND SATIETY CENTERS: NEUROANATOMICAL AND NEUROCHEMICAL COMPOSITIONS

LH is located behind to the preoptic area and forward to the ventral tegmental area and contains several distinct neurons based on gene expression [5] and function [6, 7]. Experimental data showed electrolytic bilateral lesions of the LH leads to aphagia in rats [8, 9]; on the other hand, electrical stimulation of the LH triggers food intake [10]. In this regard, it is reported that aphagia is also induced by sections interrupting some of connections, globus between the LH and pallidus. In the rat, it has been found that all the points bwhose electrical stimulation triggers food behavior are localized in nuclei projecting towards the globus pallidus and mesencephalic tegmentum [11, 12].

The VMH, also known as the nucleus of Cajal, is a pear-shaped structure located in the tuberal region of the hypothalamus. The VMH area is involved in mechanisms subserving satiety and bilateral electrolytic lesion of VMH neurons induced hyperphagia, [13], while its electrical stimulation causes interruption of food intake in hungry animals [14].

An antagonism between hunger and satiety center has been shown. When inducing cellular glucose utilization with 2-deoxy-d-glucose, firing decreases remarkably VMH neurons. At the same time, an increase in frequency of discharge was observed at the level of the LH. However, hyperglycemia reverses these changes [15, 16].

These data indicate a negative feedback control between hunger and satiety centers. LH contains neurons activated by the β-adrenergic stimulation, inducing a reduction in hunger, while VMH neurons are stimulated by α-adrenergic agonists, inducing food intake in satiated animals [17]. It has been observed that, physiological conditions, the activation of the satiety center involves β-adrenergic receptors in the LH. On the other hand, the activation of the hunger center provokes the involvement of α-adrenergic receptors in the VMH, which exerts an inhibitory control on the satiety center [18]. These results show that the stimulating effect on food intake observed in response to intra-hypothalamic injection of noradrenaline (NA) is abolished by bilateral lesion the level of VMH [2, 19, 20]. Moreover, the administration of NAergic agonists in the LH provokes, even when intake of food, while after injection of cholinergic agonists, animal stops eating even if it is hungry. The LH is a crossroad network of nerve bundles and chemical mediating pathways and signals transport. Among the latter, we must retain mainly the nigrostriatal dopamine (DA)ergic pathway and the dorsal and ventral NAergic pathways. These DAergic and NAergic pathways play a stimulatory role in food intake, while their lesion by electrolysis or microinjection of 6-OH-DA induces aphagia [19, 20, 10].

The hunger center has a moderate influence on the satiety center and *vice versa*. Bilateral interruption of connections between VMH and LH leads to overeating and obesity, thus showing that inhibitory mechanisms arising from VMH are inhibited. However, it seems that the satiety center does not act only through its lateral connections with the hunger

center considering thet in the absence of these connections, electrical stimulation of the VMH causes inhibition of eating behavior [2, 14, 15]. Overeating can also be caused by inducing lesions behind the VMH or in the midbrain central gray substance [2]. Also, electrolytic lesions of anterior hypothalamic connections induce hyperphagia because they interrupt signals arising from neurons of the anterior hypothalamus (AH) that are under control of sexual hormones and central temperature. Sex hormones influence appetite, energy balance, and weight regulation. Estradiol inhibits food intake, while progesterone and testosterone stimulate appetite and ensure eating and storing energy during pregnancy [21]. Temperature-sensitive neurons of the AH play a vital role in modulating heat production and heat dissipation [22].

A relationship between the amplitude and frequency of meals has been demonstrated. The amplitude of a meal determined the duration of the interval which followed it. This interval is interrupted by the triggering of a new meal. The amplitude of a meal does not depend on the length of the interval which precedes it. Under these conditions, two control mechanisms must be considered: one would be responsible for triggering hunger in each meal and yet for average meal frequency, and the other be responsible for restraining hunger [23, 24]. The onset of an alimentary episode is significant in stimulating central chemoreceptors by metabolic factors [25, 26]. Hypoglycemia causes intense hunger. Patient with diabetes may exhibit a bulimic patter but the factor which triggers hunger is intracellular glucopenia.

For this reason, patients with diabetes feel hungry [27]. Neurons regulating the utilization of glucose have been called "glucoreceptors." Intracellular glucopenia induced by 2-deoxy-d-glucose triggers food intake in rats, macaque, and men, although it causes marked hyperglycemia [27, 28].

3. GLUCORECEPTORS

Administration of aurothioglucose caused selective lesion of the VMH in rats and marked hyperphagia and obesity, so it could be concluded that some neurons in this nucleus must have an affinity for glucose [29]. In this case, cellular glucose deprivation triggers food intake because it causes a reduction in the activity of the center of satiety, and therefore, attenuation of the inhibition that the latter induces tonically in the hungry center. However, it appeared that the LH also contained glucoreceptors that are involved in triggering food intake [30, 31]. The iontophoretic application of glucose modifies the firing of LH neurons, and they are sensitive to aurothioglucose [32]. Moreover, rats with LH lesion did not show food responses usually triggered by insulin or 2-deoxy-d-glucose [33]. The administration of glucose in the portal vein provoked a response of satiety in hungry dogs, which led to the belief regarding the existence of hepatic glucoreceptors informing brain centers, such as the area postrema, the nucleus of the solitary tract, and the dorsal motor nucleus of the vagus nerve, through the intermediary of the vagus nerve [34, 35].

The amplitude and frequency of meals are controlled by olfactory, gustative, and gastric signals that are responsible for food ingestion. The amplitude of meals is modified by vagus nerve lesion and olfactory bulb ablation, or interruption of olfactory-hypothalamic connections, although the olfactory bulbectomy leads rat to a crumbled food consumption. The cessation of food intake and the subjective feeling of satiety occur before metabolic deficit can be corrected. It should be noted, in this regard, that the presence of a sugar substance in the oral cavity can cause an elevation of glycemia in hungry rats. Moreover, a similar rise in glycemia can be obtained by presenting a visual signal to the hungry rat, which has previously been repeatedly associated with getting food; this hyperglycemic effect is not observed if a bilateral injection of novocaine is administered in the LH [36].

4. SENSORY INFLUENCES

Sensory influences on feeding behavior are modulated by food palatability as positive hedonic evaluation of food. All the sensory qualities, such as palatability, seem to play a role in maintaining as well as restraining food intake *via* signals that oro-pharyngeal and GI chemoreceptors send to the brain areas involved in the control of eating behavior [37]. Some food appetence and aversion are innate, such as the appetite for saccharin and the aversion to quinine in rodents. A genetic study involving rats showed that genotype induces individual differences in saccharine appetite and quinine aversion [38, 39].

Sex hormones play a modulatory role in food intake. The appetite for saccharin is increased in female than in male rats, and it is markedly reduced in female after bilateral ovariectomy. Aversion to quinine is also reduced by ovariectomy and is increased in both intact and castrated females by simultaneous administration of estradiol benzoate and progesterone [40, 41].

The circadian activity of feeding behavior has been studied in rats, showing that the threshold for a meal is higher during the night, which reduces the frequency of meals during sleep phase of the nycthemere. A lipostatic mechanism plays a role in controlling the circadian cycle of food episodes. In fact, rat is hyperphagic during the night, and caloric intake is greater than energy expenditure; therefore, there is an active synthesis of fat; this lipogenesis reduces the availability of glucose, and relative cellular glucoprivation stimulates the onset of next meal. During the day, on the contrary, there is a rapid melting of fat reserves built up the night before, and the use of fatty acids delays the need for meals. Inhibition of this lipolysis by pharmacological (propranolol, or insulin) approach causes an immediate increase in food intake by shortening intervals between meals. VMH determines the neuroendocrine cycle, which underlies alternation of nocturnal lipogenesis and diurnal lipolysis, and with this daily metabolic cycle is abolished in rats lesion of the VMH [42, 43]. Innate appetite and aversion are regulated by central nuclei of the amygdala that intervene not only in quantitative regulation of appetite and innate aversion but also in qualitative modifications due to acquired experience [44]. Indeed, rats avoided the ingestion of saccharin solution if they were previously treated with apomorphine. More specifically, unpleasant gastric effects were more evident when apomorphine was injected 30 min after the ingestion of saccharine. This

response shows the pivotal role of the amygdala in inducing taste aversion and restricting food intake [44, 45]. The amygdala takes part in processes more or less rapid satiation, as the end of desire to eat, determined by oro-pharyngeal and GI afferents that progressively suppress food intake. Electrolytic lesions of the amygdala stimulate food intake due to failure of processes involved in the gradual establishment of the state of satiety, while electrical stimulation also suppresses appetite in hungry animals. Moreover, it has been observed that amygdala stimulation can induce vomiting food already ingested. However, NAergic stimulation of amygdaloid neurons induces increased food intake, agonists while both muscarinic and nicotinic cholinergic receptor inhibit food intake. NAergic stimulation leads to increased food intake in rats previously underwent food deprivation, but it does not trigger appetite in satiated rats. Thus, NA injected into the amygdala may be thought to slow down the processes which gradually suppress food intake. In fact, the stimulation of positive reinforcement system induces NA release within the amygdala, and it is probably that this stimulation subserves the facilitating influences exerted by oro-pharyngeal and gastric afferents during food intake. Therefore, it seems that the amygdala, *via* the afferents arising from the oro-pharyngeal and GI tract, exerts two different roles by adrenergic and cholinergic neurons on eating behavior. First of all, NAergic activation of amygdaloid neurons provokes the induction and maintenance of food consuming activity. Afterward, cholinergic activation induces an inhibitory influence that induces satiety therefore, cholinergic tone activated by peripheral inputs inhibits NAergic ones [46, 47, 48, 49].

5. ENERGY REQUIREMENT

Energy requirement represents the average amount of food energy needed to balance energy expenditure to sustain normal body weight. The body has two energy needs that must be met: a "short term" and a "long term needs." If we force the animal to eat, it continues to eat all day long, but if it eats at a fixed time, it will be satiated early, and it will eat less in quantity. So there is a short-term satiety process and a long-term satiety process that overlaps the first.

In short-term satiety processes are changes in glycemia or arterio-venous glucose differences, detected by gluco-receptors that affect energy intake causing satiety or hunger. This glucostatic theory suggests that hypoglycemia induces excess food intake with consequent obesity and diabetes [50].

In addition, feeding behavior may be regulated by the adipose tissue. The discovery of leptin indicates a key role supporting the lipostatic theory. When stored fat decreases, adipose tissue releases hormones, thus increasing food intake and promoting weight gain. When stored fat increases, adipose tissue releases leptin into the bloodstream to promote weight loss and reduce food intake *via* the hypothalamic satiety center [51, 52, 53].

Amino acids (AA) are also involved in controlling feeding behavior. In fact, hyperphagia is stimulated when dietary protein content is low, while satiety is induced by high dietary protein content. Peripheral factors signalling AA deficiency or abundance to the brain induce food intake responses and food preferences. AA sensing neurons are part of neurocircuits and play a role as primary brain sensors to regulate feeding behavior. The blood-brain barrier (BBB) expresses transport systems that induce the import and export of AA. AA carriers have been identified in the BBB capillary endothelium [54]. AA sensing neurons within the anterior piriform cortex (APC) are involved in AA imbalance. In fact, APC lesions prevent the discrimination between AA-containing and AA-devoid diets in rats [55]. Moreover, decreased levels of AA in APC are observed rapidly after diets deficient in AA [56], probably *via* a reduction in levels of BBB capillary endothelial AA transport system. Finally, the AA threonine injected into the APC reduces the anorectic response to a diet deficient in AA [57]. These data indicate that APC induces anorectic responses to AA imbalanced diets.

AA dietary supplementation, comprised mainly leucine, provokes an anorectic response similar to that observed after high protein diets in rats [58]. These data indicate that hypothalamic AA sensing neurons induce this hypophagic response because intra-hypothalamic administration of AAs reduces food intake [59]. Moreover, i.c.v. injection of leucine inhibits food intake and decreases body weight, thus suggesting that brain AA levels modulate homeostatic eating-regulatory circuits [60]. The neurocircuit subserving feeding behavior regulated by AA sensing neurons is formed by APC, hypothalamic nuclei, and nucleus of the medulla oblongata. Based on c-Fos immunoreactivity, AA sensing neurons are located in these brain areas [60, 61, 62]. Therefore, AA sensing neurons are involved in a feeding-regulatory network modulating food intake, inducing hunger by low dietary protein content and satiety when dietary protein content is high.

Long-term satiety processes are activated by the chemoreception of peptides (insulin, leptin, glucose, AAs) *via* the GI system, mechanisms of brain circuits involved in feeding behavior, and oxidation of nutrients in the liver. These processes regulate all those stimuli that make the body regain weight in the long term [63]. Each adipocyte plays a critical role in physiological regulation, but when it is large, it is not sensitive to factors which release the lipids. In this case, insulin and adrenaline become ineffective. When adipocytes are bloated, the body releases lipids and carbohydrates, which are satiety factors. So autocannibalism occurs in every organism, yet there is a depletion of lipids when the organism is overweight. In the case of overweight, there is avidity of adipocytes for lipogenesis; therefore, there is a regulation at the adipocyte level, a cycle of taking and giving back to the fat cell. There are two regions in the hypothalamus that are known to play a role in hyper- or hypophagia: the LH and VMH. In the hypothalamus, it appears that the activity of LH and VMH neurons has variable excitability depending on the change of their lipid concentration by fatty acid-sensitive neurons that activate intracellular signaling pathways, inducing satiety or hungry. When the hypothalamic neuron is exposed to excess lipid, the stimulus that catches it will be ineffective. When the hypothalamic neuron is in a state of lipid deficiency, the response to the stimulus is exaggerated [64].

6. HORMONES INDUCED HUNGER OR SATIETY SIGNALS (TABLE 1)

6.1. Ghrelin

Ghrelin is an orexigenic or appetite stimulant hormone synthesized by enteroendocrine cells of the GI tract [65, 66]. It stimulates food intake and growth hormone (GH) release by binding to the endogenous ligand for the growth hormone secretagogue receptor (GHS-R) [67] expressed both in hypothalamic and brainstem nuclei [68]. Ghrelin sends signals from the GI tract to brain nuclei involved in controlling eating behavior [66, 69]. Peripherally and centrally administered ghrelin increases food intake [66]; in addition, peripheral daily administration increases body weight by reducing fat utilization in rodents [69], stimulates gastric emptying, and increases gastric acid secretion in rodents [70]. Moreover, plasma ghrelin levels are increased by fasting and reduced by oral glucose administration [69]. In addition, significantly lower basal plasma levels of ghrelin were observed in obese patients compared to lean subjects [71], as well as an increase after weight loss [72] and decrease with weight regain [73].

Vagotomy or peri-vagal application of capsaicin, a specific afferent neurotoxin, abolishes ghrelin-induced food intake, GH secretion, and the firing of neurons secreting GH-releasing hormone (GH-RH). Therefore, these data suggested that gastric vagal afferent is the primary pathway conveying ghrelin's signal for hunger and GH synthesis and release [74]. Gastric vagal afferents project to, and synapse in, the NTS of the medulla oblongata [75], affecting hypothalamic firing [76]. Immunohistochemical studies showed that the NTS contains NAergic cell group (A2), which projects to hypothalamic nuclei [77, 78]. Therefore, peripheral ghrelin signals *via* the vagus nerve reach the NTS, and by ascending NAergic projections synapse in the hypothalamic arcuate nucleus, increase the activation of NAergic neurons and stimulate feeding through α1- and β2-adrenergic receptors. In fact, NTS lesions or toxin-induced loss of hypothalamic and brainstem neurons that express the NA synthetic enzyme DA-β-hydroxylase abolish ghrelin-induced food intake, thus suggesting that brain NAergic pathways arising from NTS of the dorsal medulla oblongata to the hypothalamic arcuate nucleus play a key role in eating behavior induced by ghrelin [79].

6.2. Cholecystokinin (CCK)

CCK is a peptide hormone synthesized and released by enteroendocrine cells of the duodenum. CCK stimulates the release of digestive enzymes and bile, thereby improving digestion by slowing down gastric emptying [80]. It also serves as a satiety hormone, regulating short-term control of food intake by acting as a satiety signal [81]. Several investigations on agonists and antagonists of CCK in numerous species, including humans, confirmed this satiety effect [82, 83]. CCK injected intraperitoneally in fasted adult male rats abolishes dose-related food intake of solid and liquid diets but does not suppress water intake in dehydrated rats [84]. The signal of satiety induced by CCK reaches the brain *via* the activation of capsaicin-sensitive vagal fibers that project to, and synapse in, the NTS [85, 86] and with further projections to the PVN and VMH as "satiety center" [87]. An additional pathway of CCK peripherally secreted to the brain is the CVO AP. Indeed, circulating CCK may be sensed by CCK receptors located on the AP overlying the NTS. The reduction of food intake induced by CCK was blunted by AP lesions [88], and in vagotomized rats, CCK induced Fos activation of AP neurons, thus showing that circulating CCK provoked neuronal activity of AP neurons. These effects were prevented by the CCKB-receptor antagonists, indicating that the biological response required CCK-Rs [89]. Therefore these findings suggest that CCK-R within the AP are involved in the regulation of eating behavior. In addition, CCK is also released centrally from the dendrites of PVN neurons that act *via* an autocrine signal mechanism on VMH, thus exerting a satiety effect [87].

6.3. Glucagon-like-peptide-1 (GLP-1)

GLP-1 is a peptide hormone secreted by intestinal epithelial endocrine L-cells in response to meal intake. GLP-1 stimulates insulin secretion and inhibits glucagon release, thus reducing both fasting and postprandial glucose. Moreover, it inhibits GI motility and acid secretion and regulates appetite and food intake. Therefore, low plasma levels produce obesity, while high levels induce postprandial reactive hypoglycemia [90]. GLP-1 receptor (GLP-1R) is a protein found on β-cells and neurons. *In situ* hybridization studies reported that GLP-1Rs in neurons of the thalamus, hypothalamus, olfactory cortex, choroid plexus, and pituitary gland, mainly VMH neurons, are highly labeled, thus indicating that GLP-1R is synthesized in the brain [91]. Radiolabeled studies on Ser8GLP-1 showed that circulating GLP-1 can access the brain *via* the BBB by simple diffusion [92] and activates GLP-1Rs in hypothalamic nuclei to produce weight loss [93]. I.C.V administration of GLP-1 significantly inhibited food intake in fasted rats, and the specific GLP-1R antagonist exendin prevented the inhibitory action of GLP-1 on food ingestion. Moreover, exendin alone significantly increased food intake in satiated rats. I.C.V injected GLP-1 induced c-Fos immunoreactivity in the PVN and amygdala, two brain regions regulating eating behavior, while this response was inhibited by pretreatment with exendin, thus suggesting that GLP-1Rs were required for the biological response [94].

6.4. Peptide YY (PYY)

PYY, also known as peptide tyrosine-tyrosine, is secreted from enteroendocrine cells of the ileum and colon in response to eating. PYY reduces appetite both after peripheral and central administration and mediates its effects by its receptors: Y1R, Y2R, Y4R, and Y5R. Two endogenous forms of PYY exist, namely PYY 1-36 and PYY 3-36. Receptor subtypes, Y1R, Y2R, and Y5R, are activated by PYY 1-36, whereas Y2R is activated by PYY 3-36, and neurons of the hypothalamic arcuate nucleus express mainly Y2Rs. PYY 3-36 is released in response to food intake proportionally to ingested calories and gain access to the brain *via* CVO AP, thus modulating hypothalamic areas regulating appetite. It has been observed that peripheral administration of PYY 3-36 abolishes food intake in rats and increases cFos immunoreactivity in the hypothalamic arcuate

nucleus. In addition, the administration of PYY 3-36 within the arcuate nucleus abolishes food ingestion. In a study, Y2R KO mice showed no reduction in food eaten following peripheral administration of PYY 3-36, thus suggesting that Y2R activation mediates the anorectic effect of PYY 3-36. Similar responses have been observed in humans. These findings indicate that PYY 3-36 secreted in response to food ingestion acts *via* Y2R expressed in the arcuate nucleus [95]. Patients with bulimia nervosa (BN) showed blunted levels of PYY after meals, thus suggesting an altered signal of PYY between the GI tract and hypothalamus in the pathogenesis of BN [96].

6.5. Leptin

Leptin is a hormone secreted mainly from adipose cells. It inhibits appetite and reduces fat storage in adipocytes. The secretion of leptin reflects the amount of energy stored in fat [97]. Leptin induces its effects by binding to leptin receptor ObRs, which are expressed in peripheral tissues and the brain. Two ObRs isoforms have been found, namely the ObRa or short leptin receptor isoform, which is highly expressed in the BBB and mediates the transport of leptin to the brain [98], and the ObRb or long leptin receptor isoform, which is localized in the hypothalamic nuclear groups and plays a role in the regulation of eating behavior and body weight *via* signal transduction [99]. ObRb receptor activated by leptin induces the intracellular response of signal transducer factors, mainly the Signal Transducer Activator of Transcription (STAT) that regulates energy homeostasis. ObRb KO mice are found to be hyperphagic, obese, and diabetic [100]. Several findings have shown that obese mice develop peripheral but not central responsiveness to leptin, thus suggesting the dysfunction of the BBB that reduces brain access to leptin and provokes increased body weight [101,102]. However, a specific transport system has shown direct access of leptin to the brain across the BBB; hypothalamic neurons within the arcuate nucleus sense leptin independently of this transport system, thus showing increased sensitivity to circulating leptin [103]. Leptin *via* hypothalamic, limbic, and brainstem ObRb regulates food intake, motivation for and reward of eating, and satiety [104]. Leptin administered to leptin-deficient mice increased synaptic density of neurons secreting the anorexigenic hormone proopiomelanocortin (POMC). Additionally, leptin decreased the synaptic density of neurons secreting the orexigenic hormone neuropeptide Y [105]. Leptin administration in patients with leptin deficiency was found to decrease food intake, and *via* striatal regions that reduce the perception of food reward, stimulate the signals inducing satiety with the decrease in body weight [106]. Fasting significantly reduces plasma leptin levels in proportion to changes in fat mass [97]. Moreover, endocrine responses to fasting include decreasing luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels with anovulation and osteoporosis, decreasing plasma thyroid hormone levels that reduce metabolic activities and body heat production, and increasing plasma growth hormone (GH) levels that mobilize energy stores [107]. The administration of leptin restores LH pulsatility and ovulatory menstruation in women with anorexia nervosa and amenorrhea [108]. Rising plasma leptin levels may signal the onset of puberty in boys, which triggers hypothalamic mechanisms that involve LH, FSH, and GH [109]. Both mice with leptin receptor mutation and men with congenital leptin deficiency have insulin resistance, and leptin treatment is required, which normalizes hyperinsulinemia, hypercholesterolemia, and hypertriglyceridemia [110]. These findings suggested that leptin plays an essential role in regulating energy homeostasis, both in the state of energy excess and energy deficiency as during fasting.

6.6. Nesfatin-1 and Oxytocin

Nesfatin-1, derived from nucleobindin-2 (NUCB2), is an anorectic peptide synthesized in the PVN, inducing the release of oxytocin (OT) and vasopressin (VP) and regulating feeding behavior, body weight, GI motility, glucose homeostasis, blood pressure, and water drinking [111, 112, 113] *via* the nesfatin-1 receptor localized in the brain and GI tract [114]. PVN-specific NUCB2 knockdown in mice increased food intake and decreased OT and VP release [115]. Central administration of the nesfatin-1 induced c-Fos immunoreactivity in neurons of PVN, SON, NTS, locus coeruleus, and dorsal raphe nuclei and reduced feeding [116]. It has been observed that immunoneutralization against endogenous nesfatin-1 increases feeding and reduces OT synthesis significantly in the PVN, thus showing autocrine actions of nesfatin-1 [111]. Moreover, the anorectic effect induced by nesfatin-1 is suppressed by OT receptor antagonist [111], thus suggesting that the anorectic effect of nesfatin-1 is mediated *via* the OT receptor.

OT has a role in regulating lactation, parturition, maternal behavior, and psychosocial interactions. In addition, it plays an important role in satiety [117, 118]. PVN, the primary source of OT, plays an important role in eating behavior because it receives signals from leptinergic and ghrelinergic neurons of the arcuate nucleus, orexinergic neurons expressing NPY and GABA, and pro opiomelanocortinergic neurons expressing the anorexigenic α-melanocyte-stimulating hormone (α-MSH) [119]. It was found that lesions of the PVN induced overeating and obesity in the rat [120], while the i.c.v. administration of OT decreased food intake and body weight and increased energy expenditure in both standard and genetically obese rats [121]. These effects have also been observed following peripheral administration of OT that signals to the brain *via* vagal afferent projections [122]. However, the anorectic effect induced by OT, peripherally or centrally injected, was prevented by OTR antagonist, suggesting that OTR was required for the biological response [123]. In addition to axonal OTergic pathways, OT is also released at the dendritic level from SON and PVN OTergic neurons, and the VMH may be the potential site of action of OT. The VMH contains a high density of OTRs but very few OTergic projections, thus suggesting a role as a local target of OT [124]. Food intake is inhibited by OT released from dendrites of SON and PVN since hunger is abolished by stimuli inducing OT secretion as suckling [125, 126]. A detailed description of OT secretion control is beyond the scope of this review [127, 128].

Table 1. Overview of the leading hormones regulating appetite with orexigenic (OH) and anorexigenic (AH) effects.

-	OH	AH
GI tract	Ghrelin	CCK/GLP1/PYY
Adipose tissue	-	Leptin
Hypothalamus	NPY/AgRP	OT/Nf1/α-MSH

OH and AH hormones. GI tract: gastrointestinal tract; CCK: cholecystokinin; GLP1: Glucagon-like peptide 1; PYY: Peptide YY; NPY: neuropeptide Y; AgRP: agouti-related peptide; OT: oxytocin; Nf1: nesfatin-1; α-MSH: αmelanocyte-stimulating hormone.

CONCLUSION

A variety of peripheral signals arising from the GI tract, including ghrelin, CCK, GLP-1, PYY, and leptin are carried to the central nervous system, some of these *via* the gastric afferent vagal nerve or *via* CVOs that lack of the BBB, and others crossing the BBB directly *via* a transporter system, in order to regulate meal size and energy requirement. In addition, OT and nesfatin-1, secreted by PVN neurons and released in large amounts at the dendritic level [124], exert anorectic effects *via* autocrine actions in the hypothalamus. Therefore, these hormones play a physiological role in eating behavior by exercising their actions in the brainstem and within the hypothalamus, including the VMH, LH, and other forebrain sites, such as the amygdala. Autonomic regulatory functions exercised by vagal afferent projections control energy balance, while hypothalamic mechanisms regulate the motivational drive to eat. Future research on hormones involved in eating behavior may address a new therapeutic approach to energy and reward regulation related to food. The balance between orexigenic and anorexigenic hormones represents a fundamental role in regulating eating behavior by the standard circuitry. Therefore, its derangement can play an essential role in developing eating disorders, such as bulimia and anorexia nervosa [129].

AUTHORS' CONTRIBUTIONS

Conceptualization, M.I.; methodology and database searching, M.I., T.M., G.L., V.A.G., E.G., G.D.P., V.T.; minor original draft preparation, M.I., T.M.; writing—review and editing: G.L., V.T. All the authors have read and agreed to the published version of the manuscript.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

Vito Angelo Giagulli Giovanni De Pergola and Vincenzo Triggiani are the editrial board memebers of the journal.

ACKNOWLEDGEMENTS

Declared none.

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