Koc. J. Sci. Eng., 5(2): (2022) 178-193 https://doi.org/10.34088/kojose.1091078

Kocaeli University

Kocaeli Journal of Science and Engineering

http://dergipark.org.tr/kojose

An Overview of Appetite Regulation Mechanisms

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Article Info

Review paper

Received : *March 21, 2022*
Accepted : *May 10, 2022*

Keywords

Appetite
Central Regulation
Food Intake
Peripheral Regulation

Abstract

Maintaining body weight is momentous in quality of life. Appetite takes an important role in establishing the balance of daily food absorption and spent energy and, accordingly, controlling body weight. There is a complex physiological control regulation in the maintenance of energy balance. The regulation of appetite is carried out by central and peripheral signals. The hypothalamus, brainstem, and reward centers, which are involved in central regulation, provide management of food absorption by integrating signals from the peripheral. Gastrointestinal hormones in the peripheral system regulate the digestion and absorption of nutrients. In the central nervous system, these hormones act as neurotransmitters. The ability to adjust food absorption in response to changes in energy status is an essential component of maintaining energy homeostasis. In cases where energy homeostasis cannot be balanced, it risks human life and causes a decrease in their quality of life. Diseases such as anorexia, which is characterized by low body weight, or obesity, which is characterized by increased body weight, may occur. A full understanding of the mechanism of appetite may offer new treatment opportunities in the elimination of diseases and complications that may develop due to these diseases. In this context, central and peripheral processes in the adjustment of food intake were reviewed in our study.

1. Introduction

Appetite, which is defined as the conscious desire for food, has a critical role in providing energy homeostasis and maintaining body weight [1]. There is a complicated physiological control mechanism in maintaining energy homeostasis. This system consists of afferent signals from the environment related to the energy requirement and efferent signals that affect the energy uptake and consumption [2]. This regulatory system maintains energy homeostasis through multiple interactions between signals from the gastrointestinal system and adipose tissue, and the central nervous system that responds to these signals [3]. In the disorder of this, basic energy homeostasis, body weight control cannot be realized and anorexia or obesity situations occur.

Anorexia nervosa is a disease that causes low body weight and is characterized by endocrine abnormalities, altered adipocyte function, and appetite-regulating hormone levels [4]. Obesity, which has become a global public health problem caused by the same systemic pathways and affects many people around the world, is characterized by increasing body weight. While obesity reduces the quality of life, it also paves the way for the formation of many diseases such as diabetes and hypertension [5].

Investigating the physiological mechanisms operating in the modulating of appetite and body weight aimed to shed light on the treatments of these emerging diseases. Recently, knowledge about energy homeostasis has increased. The discovery of peptides that take a role in the transmission of the body's energy needs to the brain, and the illumination of the brain areas involved in the processing of these signals have been noted as important advances [6]. Our aim in this review is to give information about the central and peripheral functioning of these mechanisms in appetite control.

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2. Central Regulation of Appetite Control

The hypothalamus, an important brain area in regulating homeostasis, plays an important role in appetite control [7]. In the hypothalamus, afferent signals from the intestine and brain stem are used, and efferent signals are generated to regulate nutrition. The arcuate nucleus (ARC), paraventricular nucleus (PVN), dorsomedial nucleus (DMN), ventromedial nucleus (VMN), and lateral hypothalamic area (LHA) located in the hypothalamus are responsible for these arrangements [8].

In the models of Hetherington&Ranson [9] and Anand&Brobeck [10], it is suggested that the lateral hypothalamic nucleus is the "feeding center" and the ventromedial nucleus is the "satiety center". In addition to this information, it has recently been thought that the control of energy hemostasis is regulated by neuronal mechanisms that generate signals using specific neuropeptides, rather than hypothalamic nuclei. In particular, the ARC takes a critical role in the integration of appetite regulatory signals [6].

2.1. The Arcuate Nucleus

The arcuate nucleus (ARC), which is an organ rich with capillaries and located above the median superiority, has an important role in appetite control with its location [11]. Perception of hormonal and food metabolic signals is facilitated through the median eminence in the ARC peripheral circulation [12]. Peptide YY (PYY) and glucagon-like peptide 1 (GLP-1) cross the BBB through unsaturated mechanisms while leptin and other signals are actively transported from the blood to the brain through unsaturated reactions [13, 14]. Due to fact that these transition differences, BBB has mediatory actions in the transmission of some peripheral signals.

The ARC consists of two main neurons that regulate nutritional signals and energy balance. These are anorexigenic neurons that regulate proopiomelanocortin (POMC) and cocaine and amphetamine-regulated transcript (CART) and appetite. The other neuron group is orexigenic neurons that stimulate food intake, expressing neuropeptide-Y (NPY) and agouti-related peptide (AgRP) [15, 16]. It is known that POMC and NPY/AgRP neurons in ARC have common features. Both groups of neurons generally have catabolic effects. In their activation, appetite decreases, energy expenditure increases, and accordingly, the amount of body fat gradually decreases. The NPY/AgRP-induced pathway is anabolic and causes more food intake and increased body fat with increased activity [17] (Figure 1).

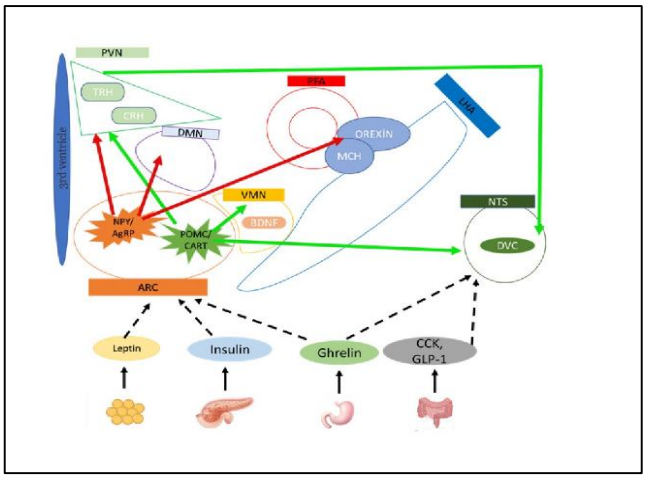

Figure 1. The ARC includes two main neurons, food intake-inhibiting anorexigenic neurons expressing POMC and CART.

2.1.1. Neuropeptide Y

Neuropeptide Y (NPY), the most numerous neurotransmitter in the brain, is part of the pancreatic polypeptide fold peptide family [18]. NPY binds to G-protein-coupled receptors named Y_1 and Y_6 [19]. It is assumed that the orexigenic effect of NPY on nutrition is mediated not by a single receptor, but by the combination of Y_1, Y_2, Y_4 and Y_5 receptors derived in the hypothalamus [8].

The NPY levels are associated with appetite in energy homeostasis. The major hypothalamic site of NPY release is the ARC [20]. While NPY release increases during fasting, it decreases after refeeding [21, 22]. NPY is more widely reflected in the central nervous system (CNS), in the hypothalamic nuclei such as the dorsomedial hypothalamus (DMH), LHA and perifornic area (PFA), and especially in the PVN [23, 24], NPY exerts its effect in appetite control by locally releasing GABA and increasing food intake by inhibiting the neighboring POMC neuron group [25]. Another effect of NPY increases the stimulation of hypothalamic Y1 and Y5, and AgRP exerts a selective antagonist effect on Melanocortin 3 (MC3R) and Melanocortin 4 (MC4R) in PVN [26]. Khrashes and coworkers (2013) found that after acute stimulation of AgRP neurons, NPY is required for rapid stimulation of feeding and, through action on MC4 receptors, the neuropeptide AgRP is sufficient to induce feeding over a delayed but prolonged period. [27].

Other studies on NPY have shown that the central application of NPY inhibits energy consumption, reduces brown fat thermogenesis [28], and suppresses sympathetic nerve activity [29]. It has also been shown to NPY is involved in the control of glucose homeostasis, and an increase in the basal plasma insulin level and especially in

the morning cortisol level, regardless of increased food intake [30].

2.1.2. Proopiomelanocortin

Proopiomelanocortin (POMC) molecule is one of the major molecules for appetite control. The amount of POMC regulation reflects the energy state of the organism [21]. Arcuate POMC neurons play a role in the regulation of energy and glucose homeostasis by sending signals to neurons located in the PVN, DMH, lateral hypothalamus (LH) and ventromedial hypothalamus (VMH) area. [31-33]. This arrangement in PVN transmits the received signal to the extrahypothalamic multiple neural networks. In this way, it creates a correlative route for energy intake and expenditure [34].

Melanocortin peptides for instance adrenocorticotropic hormone (ACTH) and α-melanocyte-stimulating hormone (α-MSH) are formed by cleavage of POMC and show their effects by binding to G-protein-coupled melanocortin receptors [35]. There are five melanocortin receptors (MC1R-MC5R), but exclusively MC3R and MC4R are transcripted in the brain [36]. MC3R and MC4R receptors are located in the hypothalamic nuclei involved in energy regulation [37].

POMC neurons are believed to suppress appetite by secreting α-MSH, an agonist of MC4Rs. In the study of Fan and coworkers (1997) with rodents, it was shown that MC4R deficiency takes a role in hyperphagia and obesity [38]. In a different study, polymorphism of this receptor was also associated with polygenic late-onset obesity in humans [39]. Most research is concerned with the regulation of α-MSH in the absence of β-MSH. However, it is supported that β-MSH acts in the regulation of energy homeostasis in humans by demonstrating those human mutations that diminish the ability of b-MSH to bind to and activate MC4R can lead to obesity [40, 41].

2.1.3. Cocaine and Amphetamine-Regulated Transcript

Cocaine and amphetamine-regulated transcript (CART) is one of the most known neuronal peptides in the hypothalamus. It is characterized in ARC, LHA and PVN [42, 43]. Many of the neurons that regulate POMC also co-regulate CART mRNA. In the fasting state, CART transcription is reduced.

In a study on starving animals, it decreases in CART mRNA was observed in the ARC while peripheral leptin administration to leptin-knock out *ob/ob* mice increased CART mRNA expression [44]. In other studies, it was observed that ICV application of CART caused a decrease in food intake [45, 46] and this application increased the CART anti-serum [44]. In contrast to these studies, it was observed that streptozotocin-diabetic rats increased their appetite for feeding after CART injection into the hypothalamic nuclei [47]. As a result of this study, it was thought that CART might have an orexigenic or anorexigenic effect in relation to the triggered neural plexus. It is also hypothesized that there may be many CART-regulating neurons in the nutritional role of CART [48].

And orexigenic neurons expressing food intake-inducing NPY and AgRP. POMC and NPY/AgRP neurons in the ARC underlie pathways that project to other hypothalamic and brain areas. These two paths often occur in parallel. The POMC-derived pathway (indicated by the green arrow) has a general catabolic effect, when active food intake decreases, energy expenditure increases, and body fat is lost if prolonged. The NPY/AgRP-derived pathway (indicated by the red arrow) is anabolic, resulting in increased food intake and increased body fat with increased activity.

2.2. Paraventricular Nucleus

The Paraventricular nucleus (PVN) in the anterior hypothalamus is the main site where corticotropin-releasing hormone (CRH) and thyroid-releasing hormone (TRH) are synthesized. There are many neural pathways involved in energy stability in the PVN [49]. The PVN is responsible for integrating neuropeptide signals from multiple CNS areas, including the ARC and brainstem. PVN is sensible to many neuropeptides included in the diet, such as cholecystokinin (CCK) [50], NPY [51], ghrelin [52], orexin-A [53], leptin [54], and GLP-1 [54]. Potent inhibition of food intake can be achieved by direct administration of a melanocortin antagonist to the PVN [55], while inhibiting the orexigenic effect of NPY administration [56]. According to electrophysiological recordings obtained from PVN neurons, it was stated that neurons expressing NPY/AgRP decreased the inhibitory GABA-ergic signal and thus stimulated food intake while POMC neurons strengthened the GABAergic signal and reduced food intake [57].

Recent studies emphasize that neuropeptides involved in appetite control might signal through a general pathway in PVN containing AMP-activated protein kinase (AMPK). Studies have shown that 2-AMPK activity in ARC and PVN can be reduced by multiple anorectic signals (such as leptin, insulin and melanocortin agonist MT-II) while 2-AMPK activity can be increased by orexigenic signals such as AgRP and ghrelin [58]. In addition, Minokoshi and colleagues (2004) suggested that peripheral hunger mediators cannot modulate 2-AMPK activity in MC4R-deficient mice and that 2-AMPK activation might be

controlled by MC4R [59].

Co-regulation of signals in the PVN plays a role in initiating changes in other neuroendocrine systems. For instance, it also affects endocrine function, such as thyroid function and therefore energy expenditure. NPY/AgRP and melanocortin released from the ARC end in thyrotropin-releasing hormone (TRH) neurons in the PVN [60]. While pro-TRH gene expression is inhibited by NPY/AgRP [61], pro-TRH expression is stimulated by α-MSH [62]. PVN also contains neurons that express CRH. The regulation of CRH, which plays a role in energy balance, is controlled by NPY signals from the ARC [63].

2.3. Dorsomedial Nucleus

The dorsomedial nucleus (DMN) is involved in energy regulation. It is known that the DMN has strong connections with the hypothalamic nuclei, especially the ARC [25]. The DMN has NPY and α-MSH endpoints and cells expressing NPY [64]. α-MSH fibers from the DMN are projected to TRH-containing neurons in the PVN [65]. In studies examining the effects of orexigenic peptides on DMN, it has been observed that NPY, galanin and GABA increase food intake when injected into the DMN [66-68]. Loss of DMN results in hyperphagia and obesity [69].

2.4. Lateral Hypothalamic Area/Perifornical Area

The lateral hypothalamic area and the perifornical area (LHA/PFA) responsible for feeding control are involved in second-order signaling. This area is where melanin-concentrating hormone (MCH) is expressed [70]. MCH mRNA level increases in fasting state, it has been proven that repeated MCH administrations increase food intake, leading to obesity [71]. Conversely, when MCH-1 receptor antagonists are administered, nutrition is reduced, as a result of a reduction in body weight [72]. In studies on mice, it was shown that the defect in the MCH gene, despite POMC and circulating leptin, increased energy expenditure and decreased hypophagia and body weights in mice [70, 73]. It has also been revealed that the perifornical area is more sensitive to feeding stimuli by NPY than PVN [74].

2.4.1. Orexin

Orexin is produced by neurons in the LHA/PFA area and zona incerta. These synthesized products are prepro-orexin peptide products called orexin A and B or hypocretin 1-2 [75, 76]. Orexin neurons exert their effects in large areas, including the dorsal motor nuclei of the vagus and PVN, ARC, nucleus tractus solitarius (NTS) [77]. The affinity of orexin A and B varies according to different hypothalamic areas. For example, the orexin-1 receptor is regulated in VMN and has a higher connection for orexin-A than for orexin B [76].

Although prepro-orexin and mRNA levels were observed to increase in the fasting state, it was determined that prepro-orexin application acted centrally with both orexigenic and general stimulation [78]. In starvation states, orexin neuropeptides can regulate a stimulation response and a feeding response to begin foraging behavior simultaneously.

The effects of MCH and orexin on energy balance have not been fully elucidated. However, strong effects of central use of orexin-A on vagal gastric acid secretion and appetite have been identified [79]. Also, Orexin is thought to function like a peripheral hormone in energy balance. It has been described that orexin and leptin receptors activated during fasting are regulated by orexin [80]. Glucose-sensing neurons in the LHA allow peripheral signals to interact [81]. Supporting this idea, some studies have shown that orexin neurons take a part in sensing glucose levels and have shown increased orexin mRNA levels [82, 83]. Additionally, peripherally administered orexin has been observed to increase blood insulin levels [84].

2.4.2. Ventromedial Nucleus

It has been known for years that the ventromedial nucleus (VMH) takes an active role in energy homeostasis. In response to projections that VMN receives from immunoreactive neurons such as arcuate NPY, AgRP, and POMC, VMN neurons signals to other hypothalamic nuclei and brainstem areas such as NTS. Studies on the food intake control of VMN show that brain-derived neurotrophic factor (BDNF) is extremely expressed in VMH [85]. A decrease in the levels of BDNF in the brain generates uncontrolled appetite while the administration of BDNF to the CNS has been found to cause weight loss in animals. In addition, BDNF is involved in the regulation of appetite, along with the co-regulation of other factors such as leptin, insulin, cholecystokinin or corticotropin. In addition, BDNF is involved in the regulation of appetite, along with the co-regulation of other factors such as leptin, insulin, cholecystokinin or corticotropin [86]. However, BDNF also affects glucose metabolism [87].

Appetite Control of the Brainstem

The brain stem has a critical role in appetite control. It regulates energy homeostasis by establishing connections with the hypothalamus [88, 89]. The dorsal vagal complex (DVC), placed in the brainstem, is very important in the

transmission and interpretation of signals from the periphery to the hypothalamus. The DVC dwells in the dorsal motor nucleus of the vagus, the postrema area, and the NTS with POMC neurons [90].

NTS has an incomplete BBB, so it easily responds to signals from the peripheral circulation, such as ARC, and to vagal afferents from the gastrointestinal system [91]. NTS includes NPY, melanocortin and GLP-1 neuronal circuits. NTS has sites where NPY binds to it, rich in Y_1 and Y_5 receptors [92]. With feeding, changes occur in extracellular NPY concentrations in the NTS, and NPY neurons are transmitted from this area to the PVN [93]. In NTS, MSH is synthesized from POMC neurons as a result of feeding and peripheral CCK administration [38]. Also, MC4R is available on NTS [37]. Regulation of an MC3R/MC4R agonist reduces food absorption while MC3R/MC4R antagonists increase it [94]. GLP-1 forms the main brainstem circuitry that regulates energy balance. GLP-1 is regulated particularly in the NTS located in the CNS, and by the mechanism it is also responsible for the expression of leptin receptors in preproglucagon neurons. GLP-1 immunoreactive neurons are then broadly projected, but less specific to the PVN and DMN, the ARC (Table 1) [95].

Table 1. Central and peripheral appetite-related hormones and peptides

Hormone	Site of secretion	Major receptors
Leptin	Adipocyte	LEPR
Adiponectin	Adipocyte, Skeletal muscle, endothelial cells, cardiomyocytes	AdipoR1 AdipoR2 T-cadherin
Resistin	Adipocyte	Unkown
Insulin	Pancreas beta cells	Insulin
Amylin	Pancreatic beta cells	AMY_{1-3}
Pancreatic polypeptit	Pancreatic PP cells	Y_4
Peptide YY (PYY)	Gastrointestinal L cells	Y_2
Ghrelin	Gastric fundal A cells	GSH-R
Glucagon-like peptide-1 (GLP-1)	Gastrointestinal L cells	GLP-1
Oxyntomodulin	Gastrointestinal L cells	GLP-1
Cholecystokinin	Intestinal cells	CCK-2

3. Peripheral Regulation of Appetite

Gut as known as the largest endocrine organ in the body is responsible for the secretion of over 30 different regulatory hormones. These hormones which interact with receptors are stimulated by gut nutrients at individual areas in the "gut-brain axis" which leads to affect hunger and appetite (Figure 2) [96].

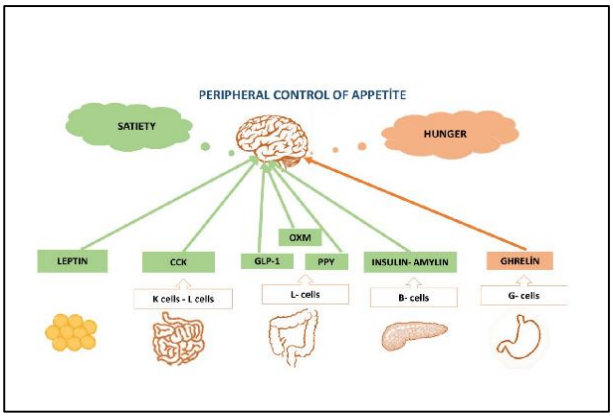

Figure 2. Demonstration of hormonal control of appetite

3.1. Leptin

Leptin is a peptide hormone and it- is originated from the *ob* gene. This hormone, which takes a part in energy balance, is specifically secreted from the adipose tissue [97]. The expression of leptin is greater in the subcutaneous than in body fat. Its concentration is parallel with the total body fat. The secretion of leptin is diminished all along with fasting and increased after feeding. The level of leptin is changed by several metabolic and hormonal factors [98].

Exogenous leptin restoration both centrally and peripherally decreases fast-induced hyperphagia [99]. Halaas and colleagues showed that with wild-type rodents, constant peripheral control of leptin diminished appetite, a deficit of body weight and fat mass [100].

Other studies, in rodents and humans, have shown that curative application of leptin can be used to correct starvation-induced changes in neuroendocrine axes [99, 101]. Hence, when the body's energy stores decrease, the response can be regulated by the leptin signal [8].

Leptin is known as a thruput of the *ob* gene that is transcribed in adipocytes [102]. However, it is expressed in the gastric epithelium [103] and placenta with low levels [104]. Leptin signals through the cytokine receptor family [105]. Through the Alternative mRNA splicing and post-translational operation, occurs multiple isoforms of the leptin receptor [106, 107]. These receptor variants could be grouped into three forms: long, short, and secreted forms [107, 108]. Long form is called Ob-Rb, and it is transcripted in the hypothalamus. However, it is located especially in the ARC, VMH and DMH, LHA and MPOA [109-111].

Pathways in the brain stem including appetite mechanisms are expressed Ob-Rb [112]. In this pathway, the domain of Ob-Rb binds to JAK-kinases [113] and to STAT. These interactions affect signal transmission and appetite mechanisms [107, 113, 114]. The expression of cytokine signalling-3 (SOCS-3)'s suppressor is induced by the JACK/STAT pathway. An *in vitro* study showed that

leptin activity blocks via reporter gene with overexpression of SOCS-3. It has been hypothesized that this re-moddelling experiment obesity-related leptin resistance and related be an outcome of boosted or enormous SOCS-3 expression. This theory lead Mori and colleagues (2004) conducted that neuronspecific depending on deletion of SOCS-3 in mice leads to in stand to diet-induced obesity. [115].This result shows, in deficiency circulating leptin is related to *ob* gene mutation [100, 116, 117].

Circulating leptin crosses the BBB [118]. It has been thought that the shorter forms take part in this leptin transportation [119]. The release of this form regulates the biological activity of circulating leptin [108].

3.2. Adiponectin and Resistin

Adiponectin, also known as adipocyte complement-related protein (Acrp30), apM1 or adipoQ, is a 244-amino acid protein released from adipose tissue [6]. Its plasma levels are higher than other circulating hormones [119].

The activity of adiponectin is essentially unexplained, but it is assumed to regulate energy balance [120]. Studies have suggested that adiponectin may contribute to insulin resistance and increase the sensitivity of peripheral tissues to insulin [121]. Additionally, Yang and colleagues (2001) conducted that adiponectin level is significantly increased after gastric partition surgery in corpulent humans [122]. The other study shows that plasma adiponectin levels in humans have been shown to be negatively correlated with body weight, body fat mass, and insulin resistance, and an increase in plasma adiponectin concentrations has been shown to occur with weight reduction in obese individuals [123]. It has also been proven by studies that the administration of recombinant adiponectin to rodents increases glucose uptake and fat oxidation in muscles and decreases hepatic glucose production [124, 125,126]. Nawrocki and colleagues (2006) in this study, it was shown that insulin resistance and glucose intolerance were observed in mice with adiponectin deficiency [127].

3.3. Amylin and Insulin

Insulin is known as a primary metabolic hormone. It is reproduced by the pancreas β-cells. This hormone is the primary adiposity signal to be defined [128]. Plasma insulin levels rest on peripheral insulin sensitivity [129]. Likewise leptin, plasma insulin level alters directly with changes in adiposity [130]. The changes in peripheral insulin levels can be interpreted by the brain as a reflection of the current level of adiposity [131].

Insulin acts as if anorectic signal in CNS. It varies the expression of some hypothalamic genes. This gene leads to the regulation of food absorption [132]. By receptor-mediated process assistance, the insulin reach the blood-brain barrier (BBB) [133]. The latest findings showed that the brain itself also produces very small amounts of insulin [134, 135]. As soon as insulin arrives in the brain, it shows as an anorexigenic signal. This signal plays a role in reducing the amount of its uptake and body weight.

Insulin is the primary modulator of an important hypothalamic circuit extending from the ARC to the PVN and is involved in the regulation of food intake and satiety [136]. Insulin receptors are expressed in the paraventricular nucleus (PVN), dorsomedial hypothalamus (DMH), and ARC and inhibit food intake through intracerebral or hypothalamic insulin administration, suppression of NPY/AgRp neurons, and activation of POMC/CART neurons [137].

3.4. Pancreatic Polypeptide

Pancreatic polypeptide (PP) is a member of the PP-fold family of peptides. It originates from the pancreas. Its expression is usually regulated along with food intake [36].

In the islets of Langerhans cells is produced PP. But also it is produced in the exocrine pancreas and distal gastrointestinal tract. Pancreatic polypeptide increases the feeling of satiety, suppresses appetite, delays gastric emptying, inhibits gallbladder movement, and plays an important role in weight loss and energy expenditure [138]. PP release occurs at a low rate in the fasted state and increases markedly during all stages of digestion. However, some other regulatory hormones such as gastric bloat or ghrelin and secretin [139 –142] lower PP levels [143]. It is also known that circulating PP cannot cross the BBB [144]. Studies suggest that peripheral control of PP reduces food absorption and energy expenditure [140]. However, studies with rodents have shown that obese rodents have less susceptibility than normal-weight rodents [145].

3.5. Peptide Tyrosine Tyrosine

The peptide tyrosine tyrosine (PYY) is a member of the PP family [146]. PYY is released from the L cells of the GI [147, 148]. PYY mainly has a the role in calorie intake [147]. Besides, PYY levels in plasma are increased rapidly after food absorption before the supplements are coined the distal intestinal L cells. It is thought that this mechanism, this sudden contact between nutrients and cells, may be the result of a neural reflex of PYY release [149].

There are two known forms of PYY, which are released by the L cells of the distal intestine $PYY_{(1-36)}$ and $PYY_{(3–36)}$. It is known that among these forms, $PYY_{(1-36)}$ has a very high closeness to the Y_2 receptor, which is a

presynaptic auto-inhibitor. Therefore, it is known as a peripherally active and very strong anorectic signal. In addition to this information, there is not enough information about the plasma amounts of $PYY_{(1-36)}$ and $PYY_{(3-36)}$ after fasting and food absorption.

Studies have shown that some stomach functions (such as pancreatic and gastric secretions delay, and gastric emptying) are disrupted or delayed with PYY application. Dysfunctions in these mechanisms have led to increased intake of fluid and electrolytes from the ileum [147, 150-152]. Peripheral application of $PYY_{(3-36)}$ has been demonstrated to prevent appetite and reduce weight gain [153, 154], and studies with rodent models of diabetes prove that glycemic control is regulated and improved [155]. In addition, it is known that PYY, unlike PP, can cross the BBB by transmembrane diffusion [156]. Studies suggest that peripheral application of $PYY_{(3-36)}$ acts as an anorectic signal, and this signal is mediated by the presynaptic inhibitory Y2 receptor on arcuate NPY neurons [157]. In addition, PYY inhibits NPY neurons with negative feedback, [153] and this inhibition reduces NPY mRNA expression [153, 154].

3.6. Ghrelin

Ghrelin is an orexigenic factor and it is secreted mainly from the oxyntic cells of the stomach. Additionally, it is released from the duodenum, ileum, caecum and colon [158, 159]. Before food intake, ghrelin levels are increased and fall after meals. As a consequence that ghrelin is known as a 'hunger' hormone responsible for food intake. With this mechanism of ghrelin, which helps to reduce the use of fat and indirectly regulates food intake, it helps to regulate body weight in the long term [160].

Murakami and colleagues (2002) demonstrated that in rats, ghrelin has the highest level at the end of the light and dark periods [161]. Growth hormone secretagogue receptor 1a (GHS-R1a) helps regulate the effect of ghrelin on appetite. This receptor is highly expressed in cells where appetite and body homeostasis are regulated. The lack of orexigenic effects of ghrelin in GHS-R knockout mice confirms this theory [162].

Ghrelin acts orexigenically and helps regulate AgRP/NPY neurons in the ARC. Generally, ghrelin is synthesized peripherally, but it is known to be expressed centrally as well. Ghrelin neurons are located between DMN, VMH, PVN and ARC [163].

Further, it is known that hypothalamic ghrelin neurons end in the LHA on neurons expressing orexin [164]. Neurons are responsible for expressing orexin stimulated by central ghrelin administration [164]. However, the physiological roles of ghrelin are not fully understood.

3.7. Glucagon-like Peptides and Oxyntomodulin

Proglucagon is generally secreted in L cells of the intestine, pancreas and central nervous system. It is also known that the neuron group in NTS secretes pre-proglucagon [165].

Different products emerge with the tissue-specific degradation of proglucagon by prohormone convertase 1 and 2 enzymes [166]. For instance in the pancreas, the primary product of proglucagon is glucagon while in the brain and intestine, oxyntomodulin (OXM) and glucagon-like peptide (GLP) GLP-1 and GLP-2 are the primary products. The product released into the circulation after food intake is GLP-1. With the expression of GLP-1, the secretion of pancreatic insulin is positively regulated. This mechanism physically regulates glucose homeostasis by acting as incretin [167].

On the other hand, OXM is released by L cells with food intake [168, 169]. Studies in rodents show that OXM acutely inhibits food absorption, regardless of central or peripheral administration [170]. This mechanism is thought to play a role in reducing body weight and adiposity [171, 172].

3.8. Cholecystokinin

Cholecystokinin (CCK) is transmitted commonly in the gastrointestinal system [173]. However, it is also known to be found in the duodenum and jejunum. There are numerous known bioactive forms of cholecystokinin. These forms can be listed as CCK-58, CCK-33 and CCK-8 [174]. CCK is rapidly released locally and into the circulation in response to nutrients, the release of CCK into the bloodstream acts on CCK receptors, causing slowing gastric emptying and increasing the feeling of fullness [175]. In addition to hunger-satiety processes, CCK functions as a neurotransmitter in various mechanisms such as reward behavior, memory loss, and anxiety [176].

CCK takes a role with the G protein-coupled receptors CCKA and CCKB receptors [177]. These receptors are known to be found in every region of the brain. CCKA receptors are generally localized in pancreatic, vagal afferent and enteric neurons while CCKB receptors are afferent in the vagus nerve and stomach [177-179].

4. Conclusion

The appetite mechanisms are a complex process that occurs when central and peripheral controls work separately and/or together. Although the studies have not been able to fully elucidate all the mechanisms, it helps in determining

the effects of food intake on physiological and biochemical processes and for further studies.

Declaration of Ethical Standards

The author of this article declares that the materials and methods used in this study do not require ethical committee permission and/or legal-special permission.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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