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ORECTIC AND ANORECTIC PEPTIDES AND THEIR IMPLICATION IN OBESITY AND THE METABOLIC SYNDROME

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Abstract

Background and aims: *Cardiovascular diseases, diabetes mellitus, the metabolic syndrome and obesity are now globally widespread clinical conditions, addressing different ages, lately extending to young and children. The causes are multiple, involving an interaction between individual genetic risk factors and environmental factors. Many studies showed the importance of the hypothalamic neuropeptides and other neuropeptides in the regulation of the balance between food intake and energy consumption. We reviewed 25 recent research studies describing the physiological and physiopathological mechanisms of the orectic and anorectic peptides and their interaction to adjust the balance between food intake and energy expenditure.* ***Conclusions:*** *The hypothalamus, through its nuclei (arcuate and paraventricular) controls the balance between food intake and energy expenditure. The proopiomelanocortin (POMC) / Cocaine and amphetamine-related transcript (CART) neurons represent the anorectic centre. The neurons that release neuropeptide Y (NPY) and agouti-related protein (AgRP) by stimulation form the orectic centre. The neuropeptide Y (NPY) is the main hypothalamic orectic neuropeptide. Its action, besides stimulating the orectic effect, is to modulate the release of other hypothalamic orectic and anorectic neuropeptides. In addition, the energy balance is regulated by adipokines released by the adipose cells, hormones and neurotransmitters, blood glucose level and other metabolites.*

key words: obesity, orectic peptides, anorectic peptides

Background and aims

Cardiovascular diseases, diabetes mellitus, the metabolic syndrome and obesity are now globally widespread clinical conditions, addressing different ages, lately extending to young and children; the causes are multiple, involving an interaction between individual risk factors and environmental factors [1,2].

Abdominal obesity, insulin resistance, increased insulin secretion, together with hypertension, dyslipidemia, hyperglycemia are risk factors of the metabolic syndrome [3,4].

The aim of this paper was to make a review regarding the involvement of orectic and anorectic peptides in the pathogenesis of obesity and metabolic syndrome. For this, we reviewed 25 recent research studies describing the

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physiological and physiopathological mechanisms of the orectic and anorectic peptides and their interaction to adjust the balance between food intake and energy expenditure.

Orectic and anorectic peptides

The importance of the obesity is emphasized not only by the many medical and social issues involved, but also by the numerous epidemiological, molecular and genetic research studies published lately. Research conducted in humans and animals show the importance of the hypothalamic neuropeptides and other neuropeptides in regulating food intake and energy consumption.

Orectic peptides

Neuropeptide Y (NPY) stimulates appetite, insulin resistance, leptin secretion (which, through a feedback mechanism, decreases the thalamic release of NPY), stimulates the secretion of luteinizing hormone, corticosteroids, stimulates the parasympathetic activity and has anti-anxiety and anti-epileptic effects [5].

Studies have shown that the NPY initiates hunger sensations, leading to hyperphagia and weight gain [6,7]. It has been shown that NPY may alter appetite, both quantitatively and qualitatively, it is involved in the carbohydrate metabolism, increasing preference for the carbohydrates [6].

NPY stimulates the insulin secretion, the hypothalamic-pituitary-adrenal activity, causing hypercorticosteronemia [6]. The prolonged administration of NPY in the third ventricle or PVN increases the hepatic lipogenesis and the secretion of insulin, and decreases the oxidative processes [6]. This results in hyperphagia, decreased thermogenesis, particularly in the brown adipose tissue. Therefore, insulin resistant hyperinsulinemia and increased deposits of fat in the adipose tissue appear [6]. For the emergence of hyperphagia and eventually obesity, there aren't necessary high levels of NPY; obesity occurs even at low levels of NPY [7].

Another orectic neuropeptide is the *agouti-related protein* (AgRP), produced by the NPY-containing neurons. Its role is to stimulate the appetite and slow the metabolism, limiting energy consumption. AgRP is one of the most durable and powerful appetite stimulants [8].

Melanin concentrating hormone (MCH) has lower orectic effect than NPY and stimulates eating behavior [6].

As for *orexins A and B*, their pathophysiological implications are not yet well known [9]. Their role is to increase the amount of food consumed by delaying the onset of satiety. The neurons that release orexins are stimulated by the lack of food, the low level of glucose in the bloodstream, so the released orexins stimulate hunger by participating in regulating the body's homeostatic needs (between the peripheral metabolism and the central control of food intake). They have lower orectic effect than the NPY and MCH. Orexin A has a stronger orectic effect than orexin B [10].

The endogenous opioids (enkephalins, endorphins, dynorphins) stimulate the appetite and the hyperphagia, increase hunger, fat and protein intake. Their action is of short duration and low in terms of quantity as compared with the effect of NPY [11].

The endocannabinoids, products of adipocytes, stimulate the appetite through their CB1 receptors in the central nervous system. The activation of the CB1 receptors also present in the periphery increases the number of adipocytes, lowers the levels of adiponectin, and increases the hepatic lipogenesis. The circulating level of endocannabinoids increases when the phenomenon of insulin resistance appears, leading to an increased appetite [12-14].

Galanine has a lower role than that of the NPY, but it has an orectic effect by stimulating

the appetite for lipids [15]. *Somatocrinin* is synthesized in the arcuate nucleus and has a pulsed release through the hypothalamic-pituitary port system in the anterior hypophysis, stimulates the secretion of the growth hormone and the appetite and the somatocrinin discharge in high doses has an inhibitory effect on food intake [16]. *γ-aminobutyric acid* (GABA) is synthesized in various zones of the hypothalamus and stimulates the appetite [17].

Dopamine is a neurotransmitter belonging to the catecholamine group, its orectic role being to stimulate the hypothalamic receptors of dopamine D1 and the release of noradrenalin [18].

Ghrelin is secreted in the stomach and intestine. The secretion increase before meals and diminishes at the end of the feeding act. It stimulates the appetite, being an orectic peptide, by activating the NPY/AgRP neurons [19]. *The peptide YY* has also orectic effect [6,19].

Anorectic peptides

There are peptides, hormones and neurotransmitters with anorectic effect which cause weight loss by inhibiting food intake [11,20].

Cocaine and amphetamine-related transcript (CART) or the peptide involved in the cocaine amphetamine regulated transcription of mRNA functions as a neurotransmitter, has an important anorectic effect by interfering with the maintenance of the body weight homeostasis [11,20].

The α-MSH and *β-MSH* (melanocyte stimulating hormones) derive from the *proopiomelanocortin* (POMC) *prohormone*. The α-MSH (melanocyte-stimulating hormone α) plays a role in inhibiting the appetite [20].

Corticoliberin (CRH) or corticotropin-releasing hormone serves to regulate the pituitary secretion of ACTH, to interfere with the stress-related endocrine behavioral responses and to inhibit the appetite [21]. *Urocortin* is a powerful appetite suppressant peptide, part of the family of corticotropin-releasing factors. The decrease in weight is due to the effect of stress on the appetite, which it is assumed that urocortin might be responsible of [21]. *Tireoliberin* regulates the secretion of the thyroid hormones, known as catabolic hormones [17]. *Dopamine*, *serotonin* and *neurotensin* inhibit food intake and induce satiety [17].

Leptin is secreted by the adipocytes and has important functions in the metabolism and the intake/energy consumption homeostasis as follows: it decreases appetite, stimulates the catabolism by stimulating the fatty acid oxidation in the liver, pancreas and skeletal muscles, stimulates insulin sensitivity, intervenes in the hepatic gluconeogenesis, influences the pancreatic β-cell function, stimulates the secretion of adiponectin, TNFα and IL-6. It reaches the hypothalamus crossing, through an active process, the blood-brain barrier, where it binds to α-melanocortin receptors and exerts its anorectic effect [22,23].

Adiponectin is produced by adipocytes and stimulates the insulin, TNFα and IL-6 secretion, stimulates the fatty acid oxidation in the liver and skeletal muscles, inhibits the hepatic gluconeogenesis, regulates the food intake and the energy expenditure and it is involved in the pathogenesis of the metabolic syndrome [23].

Insulin has a central anorectic effect, decreasing the food intake and body weight. It is secreted by the pancreatic β cells, it is involved in the glucose and lipid metabolism [23].

The peptides secreted in the digestive system also have appetite suppressant effects: *the amylin*, *the pancreatic polypeptide* (PP), *the glucagon-like peptide-1* (GLP-1), *the cholecystokinin*, *the oxyntomodulin* and *the bombesin* [19,24].

Conclusions

There is a balance between food intake and energy expenditure, coordinated by the central nervous system, the adipokines released by the adipose cells, hormones and neurotransmitters, the blood glucose level and other metabolites of food [24,25].

Eating behavior is influenced, at the central level, by the hypothalamus, but also by the brainstem and prefrontal cortex neurons and at the psychological level by satisfaction-reward, pleasure-displeasure mechanisms [5].

The hypothalamic neurons release neuropeptides with orectic effect and neuropeptides with anorectic effect [5]. Thus, the hypothalamus, through its nuclei (arcuate and paraventricular) controls the balance between food intake and energy expenditure. The POMC / CART neurons represent the anorectic centre. The neurons that release neuropeptide Y (NPY) and AgRP by stimulation form the orectic centre. The neuropeptide Y (NPY) is the main hypothalamic orectic neuropeptide. Its action, besides stimulating the orectic effect, is to modulate the release of other hypothalamic orectic and anorectic neuropeptides.

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