

Mechanism of inflammation and neuroendocrine dysregulation in obesity

Natália Tabosa Machado Calzerra^{a*}, Júlia Rafaella Resende de Almeida Dias^a, Kevin Timani^a,
Renata Layne Paixão Vieira^b, Thyago Moreira de Queiroz^c

^a Instituto de Educação Superior da Paraíba, João Pessoa, 58410407, Paraíba, Brazil. * nataliatabosa.m@gmail.com

^b Faculdade São Francisco da Paraíba, Cajazeiras, 58900-000, Paraíba, Brazil.

^c Universidade Federal do Pernambuco, Vitória de Santo Antão, 55608-680, Pernambuco, Brazil.

Received: September 27, 2019 / Accepted: November 5, 2019 / Publicado online: January 20, 2020

Abstract

Obesity is a pathological condition in which there is increased volume of adipose tissue. This state has a multifactorial and complex etiology and is a risk factor for some diseases. This research aims to address the inflammatory and neuroendocrine mechanisms involved in obesity. This is a descriptive literature review based on scientific articles, books and journals. The search used the following descriptors: adipose tissue, immune system, proinflammatory cytokines, adipokine production, and energy deregulation. In the obese state, excessive fat accumulation causes adipose tissue dysfunction that contributes to increased inflammation and altered adipokine secretion, generating imbalance in energy homeostasis and evidencing the emergence of other obesity-related diseases. In addition, hypothalamic inflammation has been associated with neuroendocrine dysregulation, favoring the development and progression of obesity. Thus, the understanding of the inflammatory aspects involved in obesity is extremely important to understand the mechanisms of energy deregulation and to assist in the prevention and treatment of obesity.

Keywords: Adipokine production, immune system, tissue, proinflammatory cytokines, leptin.

Mecanismo de inflamação e desregulação neuroendócrina na obesidade

Resumo

A obesidade é uma condição patológica em que há aumento do volume de tecido adiposo. Esse estado tem uma etiologia multifatorial e complexa e é um fator de risco para algumas doenças. Esta pesquisa tem como objetivo abordar os mecanismos inflamatórios e neuroendócrinos envolvidos na obesidade. Trata-se de uma revisão descritiva da literatura, baseada em artigos científicos, livros e revistas. A pesquisa utilizou os seguintes descritores: tecido adiposo, sistema imunológico, citocinas pró-inflamatórias, produção de adipocinas e desregulação energética. No estado obeso, o acúmulo excessivo de gordura causa disfunção do tecido adiposo que contribui para aumento da inflamação e secreção alterada de adipocina, gerando desequilíbrio na homeostase energética e evidenciando o surgimento de outras doenças relacionadas à obesidade. Além disso, a inflamação hipotalâmica tem sido associada à desregulação neuroendócrina, favorecendo o desenvolvimento e a progressão da obesidade. Assim, a compreensão dos aspectos inflamatórios envolvidos na obesidade é extremamente importante para entender os mecanismos de desregulação energética e auxiliar na prevenção e tratamento da obesidade.

Palavras-chave: Produção de adipocina, sistema imunológico, adipose, citocinas pró-inflamatórias, leptina.

Introduction

Obesity, a chronic noncommunicable disease characterized by excess of body fat, is a global epidemic because it affects virtually all age groups and social classes in developed and developing countries (Rocha *et al.*, 2019).

In Brazil, 17.5% of the population is obese and 50.8% are overweight (Santos & Ricci, 2018). About 1.5 billion Reais per year are spent on obesity treatment, including hospital admissions, medical appointments and drugs, most of which come from the government via the Unified Health System, representing 12% of the budget spent on all other diseases (Leite, De Medeiros Rocha, & Brandão-Neto, 2009).

The etiology of obesity is multi-factorial and complex, involving genetic, environmental and emotional factors, as well as lifestyle (Castro, Ferreira, Da Silva, & Oliveira, 2018). This disease affects almost all organ systems. It is associated with the development of various co-morbidities such as cardiovascular disease (CVD), type 2 diabetes and some types of cancer (Unamuno *et al.*, 2018).

The diagnosis of obesity is based on the parameter established by the World Health Organization, i.e., the body mass index (BMI), which is the ratio between body weight (kg) and height (m²). Obese individuals are those with a BMI

above 30 kg/m² (Chandrasekaran, 2018; Kumar, Abbas & Aster, 2016).

Obesity and overweight are accompanied by a low-grade chronic inflammatory state associated with increased systemic markers of inflammation. This chronic inflammation and activation of the immune system is believed to contribute largely to the development of obesity-related diseases (Maurizi, Della Guardia, Maurizi, & Poloni, 2018).

The low-grade chronic inflammatory response is a link between excess of fat and the immune system. Obesity may induce changes in immunity by altering leukocyte counts and cell-mediated immune responses (Heredia, Gómez-Martínez, & Marcos, 2012). In addition, changes in adipokine secretion along with adipocyte deregulation and the release of fatty acids into the circulation contribute to immune cell infiltration in obesity (Maurizi *et al.*, 2018).

It has also been reported that a hyperlipidic diet may induce an inflammatory process in the hypothalamus, causing interference in signaling pathways and resistance to leptin and insulin, resulting in hyperphagia, decreased energy expenditure, glucose homeostasis dysregulation, weight gain and obesity (Van de Sande-Lee & Velloso, 2012). Thus, obesity-induced inflammation poses a challenge for understanding the underlying mechanisms and how they affect metabolic systems (Saltiel & Olefsky, 2017).

The aim of this study is to conduct a literature review on the inflammatory and neuroendocrine mechanisms involved in the development and progression of obesity in order to better understand the metabolic dysregulation in an obese individual.

Obesity-induced inflammation involves multiple organs, including the adipose tissue, pancreas, liver, heart and brain (Saltiel & Olefsky, 2017). The adipose tissue plays a critical role in controlling the pathophysiological mechanisms of inflammation in obesity (Marseglia *et al.*, 2014).

The adipose tissue is divided into two types: brown adipose tissue (BAT) and white adipose tissue (WAT). The BAT has the function of heat production (thermogenesis), actively participating in the control of body temperature. This type of adipose tissue is practically absent in adult mammals. It is found mostly in newborns (Brasileiro, 2011; Coelho, Oliveira, & Fernandes, 2013). The WAT has more functions, as it is the body's main energy deposit. It stores triglycerides during energy consumption and releases fatty acids during periods of hunger. It provides mechanical protection against physical trauma and shock, contributes to gliding between the viscera and between muscle bundles, and is involved in other endocrine, metabolic and immune functions (Coelho *et al.*, 2013; Oliveira & Mafra, 2013).

To perform these functions, the adipose tissue relies on a variety of cells, such as adipocytes, which are mature cells capable of storing triglycerides, fibroblasts, immature adipocyte precursors, endothelial cells and different types of immune cells. Immune cells residing in the adipose tissue play important roles in removing molecular debris and apoptotic cells and contribute to the maintenance of tissue homeostasis (Maurizi *et al.*, 2018).

The cells that make up the adipose tissue release several biologically active molecules that locally function as autocrine

and paracrine or peripherally as endocrine (Booth, Magnuson, Fouts, & Foster, 2015), causing this tissue to regulate the metabolism of other cells or of fat cells that are located in the brain, liver, muscle or pancreas (Coelho *et al.*, 2013).

These bioactive substances secreted by the adipose tissue are called adipokines, or adipocytokines, among which leptin, adiponectin, resistin, interleukin 6 (IL-6), tumor necrosis factor (TNF- α), monocyte chemoattractant protein (CCL2 or MCP-1) and plasminogen-1 activation inhibitor (PAI-1) stand out (Brasileiro, 2011).

Inflammatory mechanisms and oxidative stress in obesity

Different plausible explanations have been proposed to explain the mechanisms relating obesity to low-grade inflammation. These include alteration in adipokine secretion by hypertrophied adipocytes, affecting macrophage activity, with a consequent additional release of proinflammatory cytokines by these cells and a stimulating effect on adipocyte lipolysis (Figure 1) (Heredia *et al.*, 2012).

Weight gain and adipocyte hypertrophy promote constriction of blood vessels in white adipose tissue, creating areas of micro-hypoxia. In this region, there is stimulation of signaling pathways that lead to the activation of nuclear transcription factor kappa B (NF- κ B), which increases the expression of inflammatory genes, causing a greater cytokine secretion and consequently recruiting macrophages to the tissue, which contributes to the generation of the inflammatory process (Leite *et al.*, 2009; Francisqueti, Nascimento, & Corrêa, 2015).

On the other hand, fatty acids released during lipolysis also activate immune cells directly and induce the production of proinflammatory mediators through the interaction with the Toll-like receptor 4 (TLR4) and other receptors of adipocytes and inflammatory cells. The activation of the TLR4 initiates the proinflammatory cascade represented primarily by stimulation of the ERK (extracellular signal-regulated kinase) and NF- κ B pathways, thereby inducing cytokine expression in various cells involved in non-specific immunity, such as IL-6 and MCP (Maurizi *et al.*, 2018).

Oxidative stress contributes to local inflammatory exacerbation, leading to adipocyte dysfunction. This effect is associated with an increased cellular metabolism due to carbohydrate and lipid overload. The increase in these nutrients stimulates the mitochondrial electron transport chain, which results in a relative hypoxia state related to a greater need for nutrient oxidation. It generates an increase in the amount of reactive oxygen species (ROS), resulting in a state of oxidative stress (Francisqueti *et al.*, 2015).

Evidence also suggests that macrophages infiltrated into the adipose tissue are involved in an increased nicotinamide adenine dinucleotide phosphate oxidase (NADPH-oxidase) and an increased ROS in the adipose tissue (Heredia *et al.*, 2012; Furukawa *et al.*, 2017). In addition, proinflammatory cytokines produced by macrophages are powerful enhancers of superoxide anion generation. Obese individuals have also been reported to be more susceptible to oxidative damage

due to low concentrations of antioxidants such as superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase, vitamins A, E, C, and β -carotene (Marseglia *et al.*, 2014). Some studies have shown that oxidative stress and proinflammatory processes are closely related, as the synthesis of ROS by adipocytes stimulates the inflammatory state (Figure 1). In addition, many immune cells produce more reactive species, contributing to exacerbation of oxidative stress (Heredia *et al.*, 2012; Marseglia *et al.*, 2014).

Oxidative stress induces damage to cell structures, including membranes, proteins and DNA. For this reason, such stress appears to be involved in the pathogenesis of various

obesity-associated diseases and metabolic syndrome (Hopps, Noto, Caimi, Aversa, 2010). Oxidative stress is known to affect insulin secretion by pancreatic β cells, glucose transport in muscle and adipose tissue. The increase in ROS production in the vascular walls is involved in the pathogenesis of atherosclerosis, hypertension and hepatic steatosis. In addition, visceral fat accumulation induces increased ROS levels, systemic lipid peroxidation and damage by excess of free fatty acids and cytokines such as TNF- α , which then further trigger systemic oxidative damage (Marseglia *et al.*, 2015).

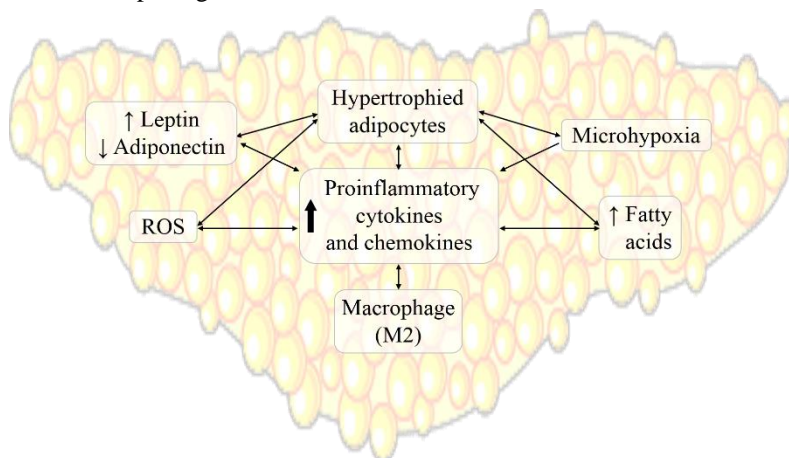


Figure 1. Mediators and inflammatory cells in obesity.

The Figure shows the relations between hypertrophied adipocytes, proinflammatory cytokines and macrophages in the context of inflammation in obesity. Hypertrophied adipocytes release inflammatory mediators and are associated with stressful situations, culminating in macrophage activation. Arrows indicate stimulatory events.

Cellular infiltrate in the adipose tissue

Several cells of the immune system play important roles in the generation of inflammatory process in obesity, among which macrophages and T lymphocytes stand out (Terra *et al.*, 2014). Macrophages, tissue-resident phagocytes, represent the largest sub-population of immune cells in the adipose tissue (40-60%) (Lee *et al.*, 2016). In addition, studies have shown that the number of such cells in humans corresponds to around 4% of the lean visceral fat, increasing to 12% when developing excess of adiposity (Mraz & Haluzik, 2014).

Obesity not only changes the number of macrophages in the adipose tissue, but also their function and distribution in tissues. Based on the expression of different antigens and cytokines, macrophages can be divided into two types of phenotypes or sub-populations: M1 macrophages and M2 macrophages, which are activated by the classical or alternative pathways, respectively (Terra *et al.*, 2014).

In the adipose tissue, the type of macrophages depends on the degree of adiposity. Lean individuals have the macrophages diffusely dispersed among adipocytes and predominantly are of the M2 phenotype. This phenotype secretes anti-inflammatory cytokines (IL-10), an IL-1 receptor antagonist (IL1Ra) and the enzyme that blocks the activity of inducible nitric oxide synthase (iNOS) (Mraz & Haluzik, 2014).

Interestingly, the increase in adiposity evidenced in obesity has been associated with an increased expression of

proinflammatory antigens and cytokines, resulting in a shift from the anti-inflammatory M2 phenotype to the pro-inflammatory M1 phenotype (Abella *et al.*, 2017). M1 macrophages are associated with the secretion of proinflammatory cytokines, including IL-6, TNF- α , IL-1 β , IL-12 and IL-23. Several factors contributing to the change from the M2 to the M1 phenotype have been identified, including lipid excess (adipocyte inability to store excess energy), adipokines and Toll-like receptor activation (TLR) (Mraz & Haluzik, 2014).

Inflammatory adipokines and cytokines

Adipocytes produce a wide range of factors grouped under the term adipokines. They regulate a variety of physiological functions related to metabolism control (Maurizi *et al.*, 2018). In obesity, there is a change associated with the release and action of these substances, which include imbalance in leptin and resistin release, increased release of free fatty acids, increased secretion of proinflammatory cytokines (TNF- α , IL-6 and IL-1), and reduction of the levels of anti-inflammatory adipokines, such as adiponectin and IL-10 (Speretta, Leite, & Oliveira, 2014). Due to the importance of the imbalance between these factors for the genesis of obesity, their main characteristics will be detailed below.

Adiponectin

Adiponectin is an adipokine secreted by adipocytes. It has an anti-inflammatory action and is involved in increased insulin sensitivity and energy homeostasis, exerting an anorectic effect (Paltoglou *et al.*, 2017). The anti-inflammatory response of this adipokine seems to be mediated by the reduction in pro-inflammatory cytokine concentrations such as IL-6 and TNF- α . This adipokine also decreases CRP levels, increases production of nitric oxide in endothelial cells, and inhibits monocyte adhesion in endothelial cells and macrophage transformation into foam cells (Maurizi *et al.*, 2018). In addition, adiponectin induces IL-10 expression in human macrophages, an anti-inflammatory cytokine (Speretta *et al.*, 2014).

Despite being produced in the adipose tissue, studies have shown that circulating adiponectin levels decrease in obese individuals. They are inversely correlated with body fat percentage in adults, showing a significant increase after weight reduction. Lower adiponectin levels are an independent risk factor for the development of type 2 diabetes mellitus, dyslipidemias and cardiovascular disease (Diwan *et al.*, 2018).

IL 10

The IL-10, an anti-inflammatory cytokine, is mainly produced by lymphocytes and macrophages. Studies have indicated that the macrophage that produces this cytokine in the adipose tissue is the M2, especially in lean individuals. Its main function is related to the regulation of the immune system, inhibiting the expression and/or synthesis of proinflammatory cytokines/adipokines. Other functions include inhibition of macrophage and T lymphocyte activity and protective effects against atheromatous plaque formation (Speretta *et al.*, 2014).

The infusion of IL-10 directly into the hypothalamus increases the sensitivity to leptin and insulin action on the hypothalamus neurons by inhibiting the inflammatory action of I κ B/NF- κ B, which results in a decreased intake and in an improvement in the control of energy balance (Speretta *et al.*, 2014).

TNF- α and IL-6

The TNF- α is a proinflammatory cytokine that can be produced by a variety of cells such as macrophages, lymphocytes, adipocytes and vascular stromal cells (Prado, Lofrano, Oyama, & Dâmaso, 2009). Its increased production and expression are due to adipocyte hypertrophy and mainly to infiltration of M1 macrophages into the adipose tissue (Speretta *et al.*, 2014). In obesity, TNF- α acts as a leptin inducer and contributes to insulin resistance. In addition, TNF- α has been found to be a powerful inhibitor of adiponectin expression and secretion (Maurizi *et al.*, 2018).

As TNF- α , the IL-6 correlates with obesity. In humans, approximately 30% of the circulating IL-6 originates from the adipose tissue at higher visceral fat concentrations compared to subcutaneous fat concentrations (Coelho *et al.*, 2013). The increase in body mass, waist circumference and free fatty acid levels correlate with increased IL-6 plasma levels (Makki, Froguel, & Wolowczuk, 2013). In addition, its production in obesity is stimulated by TNF- α and IL-1. High levels of IL-6

are associated with increased risks of coronary artery disease, atherosclerosis and unstable angina (Coelho *et al.*, 2013).

The IL-6 stimulates the synthesis of acute phase substances produced by the liver, such as C-reactive protein (CRP), and reduces adiponectin expression (Leite *et al.*, 2009). It also inhibits the insulin signaling pathway by increasing the expression of the suppressor of cytokine signaling 3 (SOCS3), which in turn is known to impair insulin-induced phosphorylation of the insulin receptor and insulin receptor substrate (IRS-1) in adipocytes and hepatocytes (Coelho *et al.*, 2013).

Monocyte chemotactic protein 1 (CCL2 or MCP-1)

The MCP-1 is secreted by various cell types, such as adipocytes, after induction of oxidative stress and inflammation or growth factors. Its level is high in obese individuals. It acts on monocyte chemotaxis at the inflamed site, contributing to the accumulation of macrophages in the fat tissue of obese people. This protein is also an inducer of cytokine expression in monocytes; in large quantities, it produces ROS and contributes to integrin expression. It has been reported that MCP-1 contributes to the reduction of glucose uptake and to the accumulation of monocytes in arteries, favoring the formation of atheroma (Makki *et al.*, 2013; Palomino & Marti, 2015).

Leptin

Leptin is a polypeptide hormone secreted by the adipose tissue. Its production and serum concentration are proportional to adipose tissue mass. This hormone plays a critical role in regulating energy balance, increasing energy expenditure and decreasing energy consumption. It acts on receptors present in hypothalamus neurons as the central signaler of satiety (Git & Adan, 2015). In addition to neurons located in the hypothalamus, other organs are sensitive to the leptin action, such as the liver, kidney, lung, pancreas and the adipose tissue (Oliveira & Mafra, 2013).

Circulating leptin binds to its receptor (LEPR) in the hypothalamus, triggering the activation of a signal transduction pathway that acts in coordination to regulate energy balance. Leptin is also considered a link between neuroendocrine and immune systems. This can be evidenced by the expression of LEPR on the cell surface of most immune cells (Pan & Myers, 2018).

Most obese individuals have high levels of leptin in the bloodstream (hyperleptinemia). However, this increase in leptin is not sufficient to inhibit appetite or increase energy expenditure because of resistance to leptin (Git & Adan, 2015; Pan & Myers, 2018). In addition, nearly 10% of the obese population has physiological levels of leptin, and even in some cases obesity has been attributed to a leptin production deficiency by the adipose tissue (Sáinz, Barrenetxe, Moreno-Aliaga, & Martínez, 2015).

The mechanisms related to leptin resistance are still uncertain, but several possibilities have been postulated: (I) failure to transport leptin across the blood-brain barrier, hindering its action on neuronal targets in the brain, (II)

inhibition of the leptin signaling cascade within specific neurons in brain areas, and (III) decreased expression of receptors of leptin. In addition, multiple factors, including inflammatory or oxidative stress processes, and diet types may contribute to resistance to leptin (Sáinz, *et al.*, 2015).

Several studies have demonstrated that mediators of inflammation and oxidative stress are related to hyperleptinemia and development of resistance to leptin (Sáinz, *et al.*, 2015). Proinflammatory cytokines, such as TNF- α , contribute to the development of resistance to leptin through additional activation of the JNK/AP-1 and NF- κ B signal transduction pathways (Jais & Brüning, 2017). Leptin resistance is suggested to occur primarily in the central nervous system (CNS) and non-peripherally, as in immune cells. This results in chronic activation of the immune system (Leite *et al.*, 2009).

In innate immunity leptin stimulates monocyte proliferation and increases the expression of activation markers, including CD38, CD69, CD25. It increases secretion of proinflammatory cytokines, stimulates NK cell development, differentiation, proliferation, activation and cytotoxicity, and induces chemotaxis and ROS production in neutrophils (Abella *et al.*, 2017; Pan & Myers, 2018). Leptin also acts on the activation of monocytes and macrophages, assisting in phagocytosis and secretion of the leukotriene B₄, cyclooxygenase and nitric oxide (Vieira, 2011).

In the adaptive immune response, leptin increases T lymphocyte and B lymphocyte proliferation. It may polarize the T lymphocyte response to the proinflammatory phenotype (TH1, which secretes IFN γ) rather than the anti-inflammatory phenotype (TH2, which secretes IL-4). It decreases proliferation of regulatory T lymphocytes and increases TH17 cell proliferation and responsiveness (Abella *et al.*, 2017). Therefore, leptin is believed to contribute to chronic inflammation associated with obesity (Leite *et al.*, 2009).

Resistin

Resistin is a protein belonging to a family of cysteine-rich proteins. It contains about 108 amino acids. Most resistin is found in macrophages and monocytes, playing a largely pro-inflammatory role. Although also expressed and secreted in eutrophic people, resistin levels increase in obese people. This increase in resistin in obese individuals causes a compromised immune response, making them more susceptible to inflammation and infectious diseases than a normal individual (Silveira, Frollini, Verlengia, & Cavaglieri, 2009). Resistin expression is stimulated by pro-inflammatory cytokines such as TNF- α and IL-6 and can induce the expression of these cytokines in the adipose tissue and peripheral blood mononuclear cells (Godoy-Matos, Cruz, Da Costa, & Junior, 2014).

Neuroendocrine dysregulation in obesity

Neuroendocrine mechanisms play a central role in balancing caloric intake and expenditure. These neural and hormonal mechanisms can be divided into three components: peripheral or afferent system, arcuate nucleus in the hypothalamus, and efferent system. The afferent system picks up signals from various locations and transmits information to

the brain stem or directly to the hypothalamus. The main components of the efferent system are leptin (produced by adipocytes), insulin (produced by the pancreas), ghrelin (produced by the stomach), peptide YY (produced in the ileum and colon), and cholecystokinin (CCK) (produced in the duodenum and jejunum) (Oriá & Brito, 2016).

The arcuate nucleus is in the third hypothalamic ventricle and is responsible for processing and integrating peripheral neurohumoral signals and generating efferent signals. The arcuate nucleus of the hypothalamus is formed by two sets of neurons that play a central role in regulating energy balance. The first produces orexigenic neuropeptides, such as neuropeptide Y (NPY) and agouti peptide (AgRP), which stimulate appetite. The other set of neurons produces anorectic neuropeptides, such as alpha melanocyte stimulating hormone (α -MSH), proopiomelanocortin (POMC) and cocaine and amphetamine-related transcript (CART), which are involved in satiety and energy expenditure. Neurons that synthesize such neuropeptides interact with each other and with peripheral signals, including leptin, insulin and ghrelin (Van de Sande-Lee & Velloso, 2012; Kumar *et al.*, 2016).

By binding to its receptor on each set of neurons, leptin inhibits neurons that release orexigenic neuropeptides and stimulates neurons that release anorectic neuropeptides. The insulin secreted by the pancreas also has an anorectic influence on the arcuate nucleus (Damiani & Damiani, 2011).

Gastrointestinal hormones are also important regulators in CNS-dependent energy control (Timper & Brüning, 2017). These include ghrelin, which is produced predominantly by gastric mucosa cells, and to a lesser extent, by the intestine, pancreas and other tissues. Ghrelin concentrations in the bloodstream increase during fasting and decrease after a meal. This hormone is known as the "hunger hormone" because it induces an orexigenic effect. It increases appetite through the action on the arcuate nucleus of the hypothalamus, stimulating the neurons that produces NPY/AgRP (Scerif, Goldstone, & Korbonits, 2011).

Another hormone involved in the regulation of ergonomic balance is the peptide YY (PYY). It is secreted by specialized cells in the gastrointestinal tract wall and presents low fasting and high levels soon after food intake (Oriá & Brito, 2016). Data have shown that PYY suppresses food intake and has an anorectic action, influencing the amount of calories eaten in meals and acting as satiety signals. This peptide reaches the CNS and inhibits NPY-producing neurons (Damiani & Damiani, 2011).

The CCK is produced by cells I in the duodenum and jejunum after ingestion of foods high in fat and proteins. The postprandial release of CCK causes a sudden reduction in the expression of orexigenic factors and at the same time stimulates anorectic factors. Thus, CCK receptor stimulation is associated with appetite suppression and satiety (Damiani & Damiani, 2011; Timper & Brüning, 2017).

The hypothalamus detects and integrates information from these hormones, which circulate at levels proportional to the nutritional status and the adipose tissue reserves. However, recent studies have evidenced the development of

hypothalamic dysfunction in obesity, which is characterized by a defective response to anorectic hormones (Jais & Brüning, 2017).

It has been described that the characteristic inflammation of obesity is associated with hypothalamic dysfunction. Neuronal inflammation and the subsequent resistance to insulin and leptin by the hypothalamus arcuate nucleus neurons disrupt this metabolic feedback, further promoting increased food intake and body weight gain (Jais & Brüning, 2017). The intake of western diets, rich in sugar and saturated fat, has been reported to induce an inflammatory response in the hypothalamus, which promotes the development of central resistance to leptin, and obesity (Git & Adan, 2015). Thus, hypothalamic inflammation has been associated with the development and progression of obesity and its sequelae (Jais & Brüning, 2017).

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