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RESEARCH ARTICLE

INSOMNIA AND OBESITY: A COMPLEX NEUROENDOCRINE RELATION INSOMNIA AND OBESITY

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ABSTRACT

Insomnia is a sleep disorder of great magnitude that significantly interferes with the homeostasis of the circadian and sleep systems. This culminates in important changes in the leptin-ghrelin axis, leading to adverse effects on the dietary choices, a consequent increase in weight and installation of obesity. The hormonal and metabolic mechanisms that promote this important change are not yet fully understood. However, it is known that a chronic process of sleep deregulation culminates in increased levels of ghrelin and decreased levels of leptin, resulting in a vicious cycle. Therefore, it is necessary to raise the population's awareness for the importance of sleep periods in order to avoid metabolic imbalances involving the development of diseases, especially obesity.

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INTRODUCTION

Hormonal factors related to appetite control and energy metabolism have always been addressed by scientific studies, especially because hormonal relations are determinant to the process ofdevelopment of obesity. In addition, the associated relation between sleep and the hormonal regulatory system of appetite, specifically the leptin-ghrelin axis, is an etiological factor that in unbalanced situations may lead to obesity (Klok; Jakobsdottir; Drent, 2017). Therefore, there is a subtle and delicate pathological relation between sleep, insomnia and the hormonal regulatory system of appetite. Such a relation demands constant attention in order to prevent any type of imbalance, since the consequences of circadian and sleep systems blockade are intense and include numerous metabolic routes, some of which may be aggravated by adverse effects on dietary choices and the consequent installation of obesity. The objective of this study was to provide a unifying panorama for future studies, generating unified knowledge to guide the improvement of comprehension efforts about insomnia and its relation with metabolic changes in the leptin-ghrelin axis.

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1. Circadian Rhythm and Sleep Regulation *versus* Insomnia

The circadian rhythm is evidenced by the sleep-wake cycle. It is divided into central circadian clock and peripheral circadian clock.The central circadian clock, generated in the suprachiasmatic nucleus of the hypothalamus (CNS), consists of approximately 20,000 neurons. Its regulation is performed by the secretion of melatonin (Welsh; Takahashi; Kay, 2010; Mohawk; Green; Takahashi, 2012) according to intracellular calcium levels (Enoki *et al*., 2017). In addition, the central circadian clock is responsible for the regulation of the peripheral circadian clock (Forsyth *et al*., 2015). The circadian rhythm lasts approximately 24 hours and is directly influenced by endogenous and exogenous factors (Forsyth *et al*., 2015, Thun *et al*., 2015). Therefore, sleep, which is considered a period of restoration and conservation of human psychosocial homeostasis closely interconnected with the circadian system, may be interrupted because the circadian rhythm plays central roles in regulating the sleep-wake cycle. In this sense, it is emphasized that sleep is divided into significantly characterized and distinct phases. The first phase is called REM (Rapid Eye Movement). It is followed by the second phase, NREM (No Rapid Eye Movement), which comprises four different stages (1, 2, 3 and 4) and corresponds to 75% of

the total sleep period (Assefa *et al*., 2015). Therefore, sleep is regulatedby mechanisms governed specifically by neuro transmitters and certain hormones, such as melatonin, whose mechanism of action is performed by the central circadian rhythm and by regulatory mechanisms specific to sleep (Gandhi *et al*., 2015). Upon understanding the regulatory magnitude of sleep, it is important to note that sleep disruptions are related to sleep disorders, with emphasis on insomnia, which is a continuous difficulty in initiating and maintaining sleep and whose symptoms must be present at least three times during the week for a period of 90 days (Harvey; Tang, 2012).

2. Circadian Rhythm: A Complex Neuroendocrine System

The circadian rhythm is defined by oscillations of biological processes associated with an internal timer (Fu; Lee, 2003). The correct functioning of this system is essential for the life of the human organism at a systemic and cellular level, covering different areas such as the sleep-wake cycle, endocrine functions (stress, growth, division and reproduction), thermoregulation, arterial pressure in systemic circulation, immune response and digestive system, associated with metabolism (Turek; Van Cauter, 1994, Zee; Attarian; Videnovic, 2013). This system is hierarchized into a central system (suprachiasmatic nucleus) and peripheral clocks (all organs and individual cells in the body) that have a synchronized or independent relation according to physiological situations (Eckel; Corsi, 2013). The central system consists of three parts: entrance path (retinohypothalamic tract, intergeniculate leaflet and raphe nuclei), central pacemaker (suprachiasmatic nucleus), and exit pathways (different areas of the cortex, pituitary and cranial nerves) (Chan *et al*., 2012). The rhythm is generated endogenously.Therefore, under conditions in which there are no influences from the outside world (constant conditions), the circadian system will continue to generate daily rhythms. Stimuli to the entrance ways are environmental signals such as external light. Their importance lies in the influence they exert on the association between the generated internal rhythm (periodicity) and the rhythm of the environment (day or night) (Pittendrigh; Daan, 1976). Endogenous generation of rhythm in men occurs by a negative feedback mechanism within pacemaker cells throughout the brain and the body. Such feedback system contains proteins produced by known "clock" genes inhibiting their own transcription and leading to daily oscillations. Clock genes are divided into positive (BMAL1 and CLOCK) and negative (PER1, PER2, PER3, CRY1 and CRY2).The positive group is responsible for activating the trigger signals of the system and the transcription of the negative group that inhibited the rhythm (Hastings; Herzog, 2004).

At the central level, an important connection of the system is made with the hypothalamic-pituitary-adrenal (HPA) axis through synapses performed by the HPA between the suprachiasmatic nucleus and the ventricular nucleus, which contains neurons responsible for the production and release of hormones, among them corticotropin-releasing hormone (CRH), responsible for the activation of the pituitary-adrenal axis (Yeh, 2015). At the peripheral level, the bidirectional relation between the molecular circadian rhythm and its metabolism is highlighted. Studies point to asynthesis of nucleotides and hepatic ribosomes resulting in circadian rhythms associated with an evidence of NAD (Nicotinamide adenine dinucleotide) oscillation, which controls rhythmic mitochondrial oxidation (Nakahata *et al*., 2008; Nakahata *et al*., 2009). The relationship is called“bidirectional” because the clock may also be influenced by the metabolism.New research points to the influence of NAD in opposition to CLOCK genes and changes in the PER2 and BMAL1 genes. Glucose mayalso affect the circadian rhythm because ofits contribution in controlling the PER2 gene activity (Kohsaka; BASS, 2007). The relation glucose-circadian rhythm is evidenced bythe inference according to which people with sleep disorders are more likely to develop diabetes in the long term and patients already with diabetesexperience difficulty in controlling the disease (Voigt *et al*., 2014). One of the hormones which ispart of the circadian production is Serotonin.Its production in axons arise from brainstem raphenuclei. Each of these nuclei, in particular the midline pontomesencephalic dorsal raphe nucleus, is surrounded by brainstem anatomical landmarks (Paxinos; Watson, 2005; Jouvet, 1999). The 5HT is stored in the vesicles inneuron terminals until its release into the synapse, where firing rates show ultradian and circadian variability (Hampp; Albrecht, 2008).

One of the main functions of serotonin, besides affecting humor, is the control of appetite and satiety (5-HT 1B and 5-HT 2C receptors) between meals (Blundell, 1992). Adequate levels of serotonin allow a greater control over the ingestion of sugars, which explains its use for weight control (Ferreira; Gomes, 2009). The analysis of different species showed a strong relation between anincrease in post-synaptic activity of serotonergic receptors and a decrease in the amount of food ingested between meals (Cambraia, 2004). Thishormone is found at reduced concentrations in anorexic patients due to the low protein intake, leading to a low availability of matter for hormone synthesis (amines) (Yakabi *et al*., 2010).

3. Leptin and Ghrelin and their Important Roles in Appetite Control

Leptin is a peptide composed of 167 amino acids essentially secreted by adipocyte cells. It is also found in other tissues, such as the placenta, mammary glands, ovary, skeletal muscles, stomach, pituitary gland and lymphoid tissue (Park; Ahima, 2015). The main function of this hormone is to suppress food intake, and consequently to increase energy expenditure through signals sent directly to the hypothalamus, thus causing anorexigenic effects (Thackray *et al*., 2016) attributed to the binding of leptin to its specific receptor (LepRs) (Park, Ahima, 2015). There are four isoforms of leptin receptors responsible for the transport of thishormone (LepR) and the performance of its functions (LepRb). By considering this information, the binding of leptin to the LepRb receptor allows the activation of JAK 2 (tyrosine kinase - Janus kinase 2), which results in the phosphorylation of three differenttyrosine residues. In addition, LepRb activates and recruits a differentiated sequence of signaling proteins (Morton; Schwartz, 2011; Park; Ahima, 2015), which include JAK 2 signal transducer, transcription activator 3 (STAT 3), insulin receptor substrate (SHP2), phosphatidylinositol 3-kinase (PI3K), SH2 composed by tyrosine phosphatase 2 (SHP2) and activated by the MAPK pathway (mitogen-activated protein kinases), AMPK (5' adenosine monophosphate activated by protein kinase), ACC (Acetyl-CoA carboxylase) and other pathways (Park; Ahima, 2015). The above mentioned agents comprise the leptin signaling cascade, which is terminated by the induction of the cytokine

signaling suppressor 3, also called SOCS3, responsible for inhibiting the JAK2-STAT3 pathway by a negative feedback circuit. It is important to remember two factors: protein tyrosine phosphatase 1B (PTP1B) is also related to the inhibition of leptin signaling, and the activation of JAK2-STAT3 signaling plays a key role in the leptin's ability to regulate energy homeostasis (Park, Ahima, 2015). The amount of its secretion is conditioned to the mass of body fat. Therefore, in obese individuals, the concentrations of this hormone are high, suggesting a resistance factor related to the inflammatory process generated by obesity (Park; Ahima, 2015; Thackray *et al*., 2016). This may be associated with a decrease in the functional potential of this hormone (Thackray *et al*., 2016). It is also verified that the secretion of leptin is influenced by the circadian rhythm. There are lower levels of it in the afternoon and higher levels at midnight (Park; Ahima, 2015). It is also emphasized that the levels of this hormone increase due to weight gain, level of circulating insulin, presence of glucocorticoids, and acute infections and inflammatory markers (cytokinins). On the contrary, its levels decrease during fasting, adrenergic stimulus and according to the levels of growth hormone (GH) and thyroid hormones, melatonin and smoking (Al-Suhaimi; Shehzad, 2013).

When considering the relevance of anorectic hormones on appetite control, a direct relation between leptin and insulin is observed, the latter being a pancreatic hormone with functions similar to the leptin hormone as to secretion potential and functions performed. Other important relations involving leptin are observed with regard to the activation of orexigenic neurons, such as POMC and CART, and a consequent decrease in NPY/AgRP synthesis. However, during fasting periods, this relation is inversed, which culminates in the increase of food ingestion and the decrease in energy expenditure, a process called positive energy (Park, Ahima, 2015). Ghrelin is a peptide composed of 28 amino acids synthesized mostly by stomach cells (in the oxyntic mucosa), but also formed in the central nervous system, kidneys, placenta and heart. It is signaled in the GHS-R region of the brain by leptin-like endocrine pathways (Mihalache *et al*., 2016). Ghrelin, in its metabolic context, interacts with other appetite-controlling agents by binding to its specific receptors in the CNS, which allows increasing the activity of NPY/AgRP neurons. Antagonistically, it inhibits POMC neurons by a pre-synaptic release of gamma-aminobutyric acid (GABA) (Mihalache *et al*., 2016). This is a hormone that has two circulation forms: acylated (GA) and non-acylated (GNA). The functions under the control of appetite, and in relation to increased appetite, are attributed to the GA form, although it is found in the circulation at a concentration not higher than 10-20%. This difference is related to the passage through the blood-brain barrier. Acylation (removal of the NH_2 group) assists in the transport of ghrelin, performing an essential function in the release of growth hormone (GH), which is related to the hypothalamus and somatotropic cells of the pituitary gland. It also assists in the stimulation of lactotrophic and corticotropic secretion, in the control of acid secretion and in gastric motility. It influences the endocrine pancreatic function and the glucose metabolism, highlighting its role in orexigenic activity coupled with control of energy expenditure (Muller *et al*., 2015). Thus, the role of ghrelin in energy expenditure is based both on an increase in appetite and on its decrease. During periods of fasting and hypoglycemia, ghrelin is increased, which signals the onset of food intake. It is immediately decreased during the postprandial period.However, it is important to emphasize that such levels can be changed according to the composition of the nutrients present in the food (Romero; Zanesco, 2006). This condition that can be confirmed by numerous studies,which identified an inverse relation between ghrelin levels and energy intake (Júnior *et al*., 2012). As regards its concentrations, they also depend on the period of food intake. Therefore, ghrelin is increased during the pre-prandial period and decreases soon after meals. This indicates the important role of ghrelin in the coordination of the time of a meal. Such finding can be observed in studies addressing the peripheral or the central administration, a factor that is independent of GH and in which there is a decrease in lipid oxidation and an increase in food intake and adiposity. Its concentrations still seem to be involved with acute and chronic changes in the nutritional status of individuals: it is high in anorexia nervosa and low in obesity (Mihalache *et al*., 2016).

Conclusion

Sleep disorders influence consistently the quality and the number of hours spent sleeping, especially insomnia, the subject of this study. It is an important condition related to the etiology of severe metabolic changes in the leptin-ghrelin axis, which are associated to an increase in overweight and to the development of obesity due to an increase in adiposity.

Conflicts of interests

The authors declare no conflicts of interests.

Authors' contributions

LABMM: drafting and conducting the review, writing; primary responsibility for final content.
NCC: conducting the review and writing.
JPTB: writing.
LSN: writing.
JCS: conducting the review; primary responsibility for the final content.

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