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Neurology & Neurotherapy Open Access Journal
ISSN: 2639-2178

Endocrinology of Sleep and Appetite

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Thesis

Volume 4 Issue 2

Received Date: November 20, 2019

Published Date: December 16, 2019

DOI: 10.23880/nnoaj-16000141

Abstract

Sleep is an indispensable restoration process for organic homeostasis and endocrine regulation, which consists of 2 phases: REM and NREM, the latter consists in turn of 4 stages, being in the N3 stage of non-rapid eye movement sleep (NREM) where hormonal secretion takes place. Circadian rhythms are responsible for the sleep-wake and feeding-fasting cycle, as well as endocrine regulation, within the suprachiasmatic nucleus, which is usually modified by different factors, causing them to be disrupted causing changes in the same way. Although the sleep process is essential for organic homeostasis, it is currently considered a waste of time for many young adults, so it is becoming a more common problem, the emergence of sleep results in changes in hormones regulators of sleep and appetite, resulting in chronic degenerative diseases, among which is obesity, as it is well known that these diseases generate high costs in health care due to the multiple complications that they bring with increasing the morbidity and mortality rate, for which it is essential to create health strategies. The objective of this study was to collect the most relevant data that allow us to demonstrate the relationship between sleep and hormones involved in its regulation; as well as its relationship with food intake.

Keywords: Sleep; Circadian Rhythm; Receptor; Feeding; Leptin

Introduction

Sleep is a physiological state, characterized by a decrease in consciousness, reversible, regulated by the surrounding rhythms; these two are carried out in the suprachiasmatic nucleus, it is essential to carry out various functions such as memory consolidation, restoration of Tissues and endocrine regulation.

Neuroendocrine regulation is carried out in stage N3 of NREM sleep, in various areas of the Central Nervous System (CNS), including the hypothalamus, area involved

in sleep and food regulation, as well as organic homeostatic regulation, involved in the latter, circadian rhythms, which, due to fluctuations in these hormones as well as changes in the sleep-wake, feeding-fasting cycle, usually present disruption and therefore contribute to the generation of chronic diseases.

In recent years, various strategies and treatments to combat obesity have been sought and generated, in the same way, it has been the main topic in multiple investigations in which appetite and sleep regulatory hormones are related. The purpose of this review is to show the most recent research related to regulatory hormones, giving guidance to the generation of new research involving both neuropeptides, for the establishment of new treatments.

The objective of this review was to gather the most current information about the hormones that regulate sleep and their relationship with appetite.

Methodology

A search was made in different databases PUBMED, EMBASE, DATABASE, in relation to hormones related to sleep and appetite, determining the period of publication from 2013 to 2018, with the exception of base studies showing historical part of the document. Publications were specified in different languages that included Portuguese, English, Japanese, Russian, Spanish. The terms used for the search included sleep, hormones, appetite, Obesity, physiology, neurophysiology, neurobiology, biosynthesis, endocrinology, circadian Rhythm, receptor, feeding, leptin, Melatonin, cortisol, orexin, ghrelin, POMC, AgRP, NPY, obestatin, serotonin, Dopamine, norepinephrine, epinephrin, GABA and the Boolean operators AND, OR. Finding a total of 12,578 articles of which were discarded based on the title, reading of the summary and content leaving a total of 200 articles included.

Sleep Overview

Sleep is a reversible physiological state, characterized by decreased consciousness and low perceptions of the environment, where relaxation and postural changes muscle are involved, presenting with a circadian periodicity [1-3]. Which aims at molecular replacement, memory consolidation [4] restoration of metabolic processes and tissues, waste disposal promoting organic homeostasis [1,5,6].

Regulatory factors such as endocrines are involved in these repair and homeostasis processes, due to the fact that environmental factors, demands for sleep-wakefulness, feeding-fasting or stimuli-internal responses from target tissues show fluctuations of various hormones; same that are directed by circadian rhythms [4,7,8].

Circadian rhythms generated in the suprachiasmatic nucleus (NSC) [9,10] are essential to maintain physiological mechanisms under sleep regulation, which comprises 2 phases, one consisting of rapid eye movements (REM) and one of the non-rapid eye movements (NREM), [11] with a duration of 60 to 90 minutes each, [12] going through different stages of wakefulness, N1, N2, N3 and R, considering N1 to N3 characteristic of the NREM phase. In stage N3 the sleep is deep and the awakening in this period is difficult, here the tissue repair is carried out in addition to strengthening the immune system [13].

The cortical activity comes from corticotalomocortical interconnections, involving a series of neuronal assemblies, which involve the synchronization and desynchronization of the cortical activity itself that distinguishes the NREM dream for awakening and REM sleep [14,15]. Daily sleep is preceded by waking rhythms, which arise from the interactions between the circadian cycle regulated by the hypothalamus and a sleep homeostat, of which its anatomical control center has not been recognized. However, it is known that this sleep-wake cycle involves multiple systems and that these are dependent on internal and external regulators [16].

An imbalance in the sleep-wake cycle brings oscillations in the hormonal levels that regulate food intake, being proposed as one of the main causes of obesity and diabetes [10,17-22].

Sleep Metabolism

The metabolism is an essential component for the health of living beings; Thus, metabolic health depends largely on the lifestyle of each individual, where sleep health is a primary part of the repair processes in each of the body systems and is essential for the restoration of the central nervous system and its functions [23]. Alterations in physiological sleep, such as those changes in sleep patterns associated with endocrinological changes or diet and age, can have consequences that affect the biological clock that is the center of circadian regulation of sleep and therefore can influence the food

intake, energy expenditure and body fat. During evolution, mammals have developed endogenous clocks, characterized by cycles of approximately 24 hours called circadian clocks; which, are maintained by a regulator in the central nervous system (CNS) at the level of the hypothalamus, the suprachiasmatic nucleus (SCN) [24]. The SCN as the main regulator is able to synchronize changes in our body, thanks to the induction of external factors such as light information that serves as the most powerful synchronizer [25]. In contrast, food has a synchronizing influence on the SNA, [26] with the exception of foods with high palatability [27]. So the modification or alteration in any of them is capable of inducing disease in humans.

The SCN receives information from the nerve cells located in the retina that detect the light to regulate the circadian rhythm and regulate sleep through the activation of multiple pathways allowing the nocturnal release of ACTH, prolactin, melatonin and norepinephrine. One of the most commonly recognized pathways by which this occurs is through the simulation of the release of norepinephrine by the CNS, which in turn stimulates the pineal gland to release melatonin [28].

It has been shown that insufficient sleep and feeding in inadequate circadian times have been identified as risk factors for weight gain, prevalent in modern society, McHill, et al. [29] Investigated how chronic insufficient sleep impacts the circadian moment of hunger. subjective and fasting metabolic hormones; in a 32-day randomized single-blind randomized control study, in healthy participants (range, 20-34 years) randomized distributed under two conditions (control group and sleep restriction group (CRS) of 4.67 hours of sleep. Participants lived in a "20 h day" designed to distribute all behaviors and food intake equally in all phases of the circadian cycle every six consecutive days of the 20 h protocol. For every 20 hours a day, participants received an isocaloric diet designed by a nutritionist consisting of 45-50% carbohydrates, 30-35% fat and 15-20% protein adjusted for sex, weight and age Non-numerical subjective assessments of hunger were recorded before and after meals , and fasting blood samples were taken 5 minutes after waking, subjective hunger levels and fasting concentrations of leptin, ghrelin, insulin, glucose, adiponectin and cortisol they showed circadian patterns; however, there were no differences between CSR conditions and control in subjective hunger ratings or any fasting hormone concentration. These findings suggest that chronic insufficient sleep may have a limited role in altering the robust circadian profile of subjective hunger and fasting metabolic hormones [29].

Among the various studies conducted in recent years it has been seen that there are hormones related to sleep; one of them performed by Blouin, et al. [30] in laboratory and human rats, where changes in the levels of two hypothalamic neuropeptides, hypocretin-1 (Hcrt-1) and melanin concentrating hormone (MCH), in the amygdala were measured human They showed that MCH increased at the beginning of sleep induction; while Hcrt-1 levels increased in the induction of wakefulness, so it is thought that these hormones are involved in the induction and stabilization of sleep [30,31].

Melatonin

Melatonin is a hormone activated during the dark, synthesized by pinealocytes from 5-hydroxytryptamine, cataloged as an indoleamine because it contains an indole ring, replaced by an amino group [32]. Melatonin exerts its effects thanks to two membrane receptors coupled to G protein (MT1 and MT2), expressed in various areas of the central nervous system (CNS), [33] such as the suprachiasmatic nucleus (NSC), hippocampus, prefrontal cortex, ganglia basals among others; as well as in various peripheral organs [34]. By this, the receptors promote changes in cell signaling that involve the regulation of pubertal development, [35] seasonal adaptation [36] and the sleep-wake cycle, [37] so that the alteration of these receptors and Melatonin production is manifested by surrounding disorders of sleep, memory and learning; [38] in addition, she is involved in the progression of chronic degenerative, metabolic and obesity diseases [39].

The maximum concentration of melatonin is during stage N3 of NREM sleep, [36] produced and secreted by the pineal gland through a signaling pathway that goes from the suprachiasmatic nucleus who acts as a receptor of light from the retina [6,37] to the paraventricular nucleus towards the upper thoracic spinal cord and from there to the cervical ganglion [38,39] following a zirconic pattern, this melatonin will activate the MT1 receptors factor that induces neuronal inactivation related to induction of sleep, [40] while MT2 has been linked to neuronal activation in the NSC [41].

It seems that the mechanism of melatonin once coupled to its specific ligand in the MT1 receptor, allows this receptor to combine with Gi / $_{11}$G proteins and Gq / $_{11}$G protein, inhibiting cAMP, stimulated by phosphocholine, signaling protein kinase A and phosphorylation of CREB. In addition, it increases mitogen-activated protein kinase½ and kinase½

regulated by extracellular signals, potassium mediated conductance; on the other hand, MT2 seems to exert the opposite action [33] which would appear that the activity of melatonin is self-regulated in itself and is dependent on binding to the specific type of receptor.

This mechanism of the MT1 and MT2 receptors plays an essential role in the circadian rhythm [42] and in the secretion phase of melatonin, so an increase in this phase contributes to the disruption of the surrounding rhythms, causing a delay in them and decreased sleep time, [33,43] which results in various chronic degenerative diseases [40,33,44], such as diabetes and obesity [45-49].

In a study conducted in male rats of the 10-month-old Sprague Dawley strain for 12 weeks, by Wolden-Hason, et al. [50] it begins investigations into possible mechanisms that involve daily administration of melatonin with suppression of intra-abdominal visceral fat, showed a 7% reduction in body weight, so it is considered that the decrease of melatonin by age leads to the development of obesity [50].

Cortisol

In contrast to melatonin, Cortisol prepares the body for wakefulness, being at higher levels during the light phase, [7] is associated with stress and is produced by the adrenal cortex [51]. The levels of this hormone fluctuate with the sleep-wake cycle [52], it is believed that low cortisol levels during deep sleep lead to sleep inertia [53-55]. Some studies mention that a decrease in sleep hours elevates cortisol, causes an overload of glucocorticoids and as a consequence pernicious effects on the body [56,57], such as obesity since interacting with insulin allows the accumulation of triglycerides and leads to an increase in central adiposity [58].

Cortisol is synthesized by cells in the fascicular zone of the adrenal cortex by stimulating adrenocorticotropic hormone (ACTH) [58,7]. In addition, it has been shown that cytosines or adipocytes also stimulate the hypothalamus, pituitary, adrenal axis, through its three levels, hypothalamus, anterior pituitary gland and adrenal cortex. The cortisol produced under this activation is transported bound to the corticosteroid binding globulin at the plasma level and is directed to the peripheral tissues, remaining available by the action of the enzyme 11β-hydroxysteroid dehydrogenase, also being able to bind to the glucosteriodes receptor forming a complex which translocates to the nucleus, modulating the transcription of the genes that respond to cortisol [59].

In experimental animals it has been observed that the pathway that activates melatonin formation is capable of activating the hypothalamus-anterior pituitary-adrenal cortex axis through the transmission of light from the retina to the suprachiasmatic nucleus (NSC) that sends the signal to the hypothalamus medial dorsum (HDM) and periventricular nucleus and from there to the dorsal part of the paraventricular nucleus (NPV) and medial parvocellular nucleus along with corticotrophin-releasing hormone (CRH) neurons to stimulate the secretion of adrenocorticotropic hormone (ACTH) that will stimulate the adrenal cortex for corticosterone secretion [60].

Cortisol maintains glucose balance, inflammatory responses [61] is responsible for controlling the metabolism of lipids and proteins [62]. Tomiyama, et al. [63] evaluated in 45 women with obesity and healthy weight stigmatization associated with physiological risk factors related to stress and obesity, finding a significant relationship between weight stigma and central obesity with cortisol levels [63] Another study by Himmelstein, et al. [64] in 110 women with Body Mass Index (BMI), where the relationship between weight stigma and psychological and physiological consequences was assessed, a significant relationship was found between weight perceptions with a sustained cortisol elevation, these Results suggest that elevated cortisol levels are a factor that stimulates eating and contribute to obesity [64].

On the other hand, Lucaseen, et al. [65] assessed the relationship of the sleep chronotype, food intake, endocrine and metabolic parameters in 27 men with obesity and 92 postmenopausal women, both with lack of sleep for 6.5 hours. An elevation of morning ACTH plasma levels is found in those with evening chronotype and those who add obesity as a variable are associated with a greater tendency to increase cortisol [65].

Studies in experimental animals determine that cortisone and cortisol promote the production of leptin by associating directly with its plasma concentration; that is, the higher the concentration of cortisol, the higher and the concentration of plasma leptin [66].

Leptin

Leptin is a hormone with anorexigenic function, produced mainly in adipocytes, and secondarily in other tissues such as the mammary gland, ovary, among others [67]. Various research works have linked her to functions such as appetite regulation, as a mediator in the reward for food and energy expenditure; [68,69] as well as, it has

been involved in glucose homeostasis [70] and in the initial phase of sleep where there has been an increase in the levels of said hormone [71].

Within its mechanism of action, an activation of the pro-opio-melanocortin neurons (POMC) and the cocaine and amphetamine transcript (CART), related to the suppression of food intake, has been proposed through the inhibition of the peptide related to Agouti (AgRP) and neuropeptide Y (NPY) [69,72-74]. So that the activation of POMC reacts by enzymatic cleavage, to derive in ACTH (adrenocorticotropic hormone), stimulating the HHA axis, for cortisol secretion [75]. It seems that this activity is influenced by the aging process, gender [76] and the stress response [77] as well as, for exercise, food and sleep among other factors [78-80].

It seems that when the secretion of leptin is modified, it affects functions such as the processing of the ingested nutrients, the precision in the size of the food portion and inhibits the digestive and restrictive anabolic effects [81].

On the other hand, the loss of sleep not related to stressors influences the levels of leptin in the opposite way to the loss related to stress in which the pituitary, hypothalamus, adrenal axis will be activated leading to an increase in appetite and hormonal changes, which favors the consumption of foods rich in carbohydrates and therefore obesity [82].

Hart et. al., conducted a study in 2015 on 12 women between 25 and 55 years of age, overweight and obese, in which they examined experimental sleep changes on hunger, food intake and appetite-regulating hormones, they expected that under the restriction of sleep the leptin was at low levels, unlike the ghrelin, insulin and glucose that were expected to be elevated; however, no differences were found between energy intake and appetite-regulating hormones, only in protein restriction did protein intake rise [83]. Unlike this study in 2013, in 37 children from 8 to 11 years of age with overweight and obesity, they assessed the effect that occurs when changing the duration of sleep, on food intake, food reinforcement , appetite and weight regulating hormones, participants were subjected to decreased and increased sleep in different weeks, during the sleep increase condition there was a decrease in food consumption of 134 kcal, weight; as well as, a relationship with low fasting leptin levels in contrast to the condition of decreased sleep time, while with fasting ghrelin or food reinforcement there were no differences in both conditions [84].

Ghrelina

Ghrelin, also known as the appetite hormone, is an acylated peptide composed of 28 amino acids produced primarily in the P / D1 and X / A type cells, [85,86] at the level of the gastric fund's ointment glands, [87,88] in the duodenum, jejunum, lungs, urogenital organs and pituitary gland [89]. Its production is promoted through the union of the preproghrelin gene to the ghrelin messenger (mRNA), becoming a preprocessor of 117 amino acid preproghrelin, which is cleaved to form obestatin and ghrelin [90]. In addition, the presence of ghrelin has been detected in various brain areas such as the neurons of the hypothalamic arcuate nucleus (ARC) [91], the ventromedial hypothalamic nucleus (VMN) and the NPV paraventricular nucleus), relevant areas for the control of Hormone secretion of growth (GH) and appetite [92].

Among its functions, it promotes the release of growth hormone, intervenes in fat deposition, regulates glucose homeostasis and collaborates in gluconeogenesis / glycogenolysis, metabolism and energy expenditure, among others [93-95], It has also been seen to participate in the sleep-wake cycle, learning, memory, neuroprotective effect [96] triglyceride synthesis, modulation of reproductive functions, decreased blood pressure, modulation of endocrine and exocrine secretion of the pancreas and orexigenic [94].

Its orexigenic activity is mediated by the intestine that sends neuronal signals of hunger to the arcuate nucleus through the bloodstream where they are integrated to establish neuronal signals through vagal afferents to activate the hypothalamic circuits in the arcuate nucleus (ARC) and NPV, the dorsomedial region, the central nucleus of the amygdala and the nucleus of the solitary tract (NTS) [92,96,97], in the ARC orexigenic neurons expressing NPY and AgRP and anorexigenic neurons expressing POMC and the POMC peptide product (α-MSH) as well as cocaine and amphetamine-regulated transcription (CART) [98]. NPY binds to Y1 and Y5 receptors by stimulating food intake, while AgRP inhibits the anorexic actions of αMSH that is secreted by POMC neurons [99,100].

This signaling occurs is observed with lack of sleep, ghrelin has high rates during the night, synergizing with leptin [101] therefore the surrounding rhythms affected due to lack of sleep bring about the modification in food intake and hormonally regulated hedonic factors between relating to ghrelin as a possible causative factor [102].

A study by Szentirmai, et al. [103] In male rats of the Sprague-Dawley strain, where the effects of the administration of 0.04, 0.2 or 1 µg of ghrelin were studied by microinjections in different hypothalamic areas involved in feeding regulation and sleep (lateral hypothalamus, medial preoptic area and paraventricular nucleus) during the sleep stage. Their results showed effects that promoted wakefulness, increased food intake in addition to decreased sleep in the first hour after injection at a dose of 0.2 µg. [103].

On the other hand Broussard, et al. [104] conducted a study in 19 men with normal and healthy BMI with and without sleep restriction, in which it was evaluated whether sleep restriction alters the 24-hour profiles of ghrelin appetite regulating hormones, leptin and pancreatic polypeptide when administering a standardized diet and if these alterations predict the intake of food with an ad libitum diet, the results showed elevation of ghrelin levels with sleep restriction, an increase in caloric intake, mainly carbohydrates, thus considering that elevated ghrelin due to sleep restriction leads to increased food intake and obesity development [104]. Such results suggest that ghrelin is related both in the regulation of food consumption and the type of food ingested, indirectly related to the increase in energy consumption and that it contributes secondarily to the development of exogenous obesity.

Orexins (Hypocretins)

Orexin A and orexin B are hypothalamic neuropeptides, derived from the proteolytic cleavage of preproorexin consisting of 131 amino acids; [105-107] orexin A is composed of 33 amino acids with an amino terminal in the pyroglutamyl residue and two intra-chain disulphide and amidation bonds of the carboxyl terminal, while orexin B is formed of 28 amino acids with an aminated carboxy terminal [106, 108]. Regarding its place of synthesis, there is still great controversy. Several authors have found their expression in neurons of the hypothalamic mediolateral nucleus, hypothalamic nucleus, medial dorsum, perifornian area to lateral hypothalamus, using immunohistological techniques [107,109-112].

Two receptors have been found: OX1R expressed in locus coeruleus, [113] in ventromedial and dorsomedial hypothalamic nucleus, while OX2R is expressed in the arcuate nucleus and mammillary nucleus, OX2R has affinities to both neuropeptides, while OX1R is exclusive to Orexin A, both neuropeptides are expressed in the paraventricular nucleus of the thalamus, medial dorsal and medial tegmental area [114], it has been described that both receptors have effects on the regulation of the physiological mechanisms of energy metabolism, sleep regulator and wakefulness, [115] reward, autonomous function, [116-120] stress modulators [113] mating and behavior maternal, feeding; [121] same that may be sensitive to experience-dependent effects [116].

Orexin A and its receptor appear to have a greater participation in the regulation of intake, [121] when activated by environmental signals increase the feeding; In addition to participating in reward feeding [122]. It seems that high concentrations of glucose and leptin inhibit the activity of orexin A, while low concentrations of glucose and ghrelin allow its activation favoring food consumption [108,123].

In the dream the levels of the orexin system decrease due to the inhibitory action of the GABAergic hormones in the antero-basal brain and median ventrolateral preotic hypothalamus, they are also responsible for the control of breathing and muscle tone in the sleep phases [124]. The orexin system allows the stability of wakefulness that can be interrupted due to environmental stimulation, which is why the lack of these peptides causes loss of consciousness, seen in patients diagnosed with narcolepsy [125].

Studies in transgenic mice for orexin expression show that the pharmacogenetic activation of orexin neurons is related to an increase in locomotor activity, food intake and water. However, when ablation of orexin neurons is not found changes in the previous relationship or in the expected modifications of the regulation in the sleep-wake cycle; The authors conclude that only some neurons are required to cause the effect on the metabolism [126].

On the other hand, a study conducted by Collet et al., Where the relationship between the energy balance and the sleep-wake cycle was assessed in 12 healthy men, subjected to sleep restriction and caloric restriction for 2 days and subsequently subjected to diet Ad libitum on demand (AL), measuring the levels of different hormones, finding that leptin decreases by 20% after the restriction and an increase during AL feeding, cortisol and ghrelin levels were not affected during the restriction caloric The orexins decreased with caloric restriction maintaining a direct correlation with the duration of sleep in stage 4, these data make it clear that changes in energy levels affect the sleep-wake cycle, giving guidance to generate

new research to assess the lack of I dream about the risk of obesity [127].

Obestatin

Obestatin is a 23 amino acid peptide, a translational result of the cleavage of residues 76 and 98 of preproghrelin [128,129]. It is produced in the gastrointestinal mucosa [130,131] and in smaller amounts in pancreatic islets as well as in different tissues such as mammary gland, testicles, skeletal muscle, adipose tissue, lung, liver [132-134]. In several studies, obestatin has been linked to the GPR39 receptor, expressed in white adipose tissue, duodenum, jejunum, colon, pancreas, large and small intestine, heart, cerebellum, spleen, lungs [135]. Other studies have shown that this receptor is not specific for obestatin uptake, so controversy continues in trying to establish a specific receptor for this peptide [133,134, 136,137].

Obestatin has been linked to the decrease in food intake [129,131,136,138] as well as, with increased body weight and gastrointestinal motility, it mediates cell survival and prevents apoptosis, [131,129] gastric emptying, jejunal motility [129]. In addition, it promotes lipid accumulation, leptin secretion in preadipocytes, adipocyte differentiation, lipolysis modulation [139] and glucose uptake [140].

It is considered the ghrelin antagonist by promoting the inhibition of jejunal contraction, through an afferent vagal signal [136]. In a study conducted by Yuan et al., in experimental herbivorous carp, it was observed that by an intraperitoneal injection of obestatin, the effects of NPY and its receptors are reduced, leading to the elevation of mRNA levels of the Regulated Transcript of Cocaine and Amphetamine (CART) and POMC [141]. Therefore, it is proposed that obestatin plays a partial role in inhibiting food intake.

Several peptides involved in appetite regulation have implications for sleep; Szentirmai et al., assessed the effect of obestatin on the sleep of male rats of the Sprague-Dawley strain, applying intraperitoneal (16 and 64 μg/kg) or intracerebroventricular (1, 4 and 16 μg in a 4 μl volume) injections of obestatin, showing that in the animals treated intracerebroventricularly with the dose of 1 μg there were no changes in sleep, in those treated at a dose of 4 μg they had a decrease in REM sleep after the first three hours, while one dose of 16 μg, obestatin produced a 58% increase in NREMS sleep time one hour after administration, compared with the dose of 64 μg/kg intraperitoneally in which NREM sleep decreased in patients two hours after administration, but not at the dose of 16 μg / kg in which the sleep-wake cycle did not affect or interfere with NREM sleep, concluding that the effect shown in the dose of 16 μg by intracerebroventricular route was due to the interaction of obestatin with the central receptors [142]. It seems that these findings suggest that obestatin increases NREM sleep and decreases food intake when injected at the beginning of the activity period of rats.

Pro-Opiomelanocortin (POMC)

POMC is a polypeptide of 241 amino acid residues [143], composed of arginine / lysine and glutamate / aspartate. It is a precursor of the adenocorticotropic hormone, β-endorphin, a melanocyte stimulating hormone α, β and γ (MSH), N-POMC 1-48, β-lipotropin [144-146]. It forms part of the melanocortin system in conjunction with the neuropeptide of the regulated transcription of cocaine and amphetamine (CART), Neuropeptide Y (NPY), Agouti-related Peptide (AgRP), and gamma-aminobutyric acid (GABA) [147]. It is synthesized in the anterior and intermediate lobe of the pituitary and arched nucleus [144]. They are expressed in the arcuate nucleus of the hypothalamus and the nucleus of the solitary tract; areas where the satiety signal is perceived [148,149]. Its activity is related to glucose regulation, [150] fasting and weight loss [151,152].

The role of POMC as an anorexigenic hormone, was proposed by Zhan et al., Examined the behavior of POMC neurons by stimulation and ablation in the arcuate nucleus and nucleus of the solitary tract in POMC-Cre transgenic mice from 8 to 16 weeks of age, they found that chronic activation reduced food intake, acute activation in the nucleus of the solitary tract rapidly suppressed food consumption, as far as ablation produced hyperphagia and metabolic disorders among which obesity is found [153].

In feeding, ghrelin activates AgRP neurons in the face of energy shortages by inhibiting POMC neurons creating a “hunger boost” [151]. POMC inhibition is modulated by serotonin and leptin, [144,152,154] the latter by stimulating POMC neurons activates the central pathways of melanocortin due to the release of melanocyte stimulating hormones that in turn cause the release of α and β of melanocortins to activate the melanocortin 3 and 4 receptors (MC3R and MC4R, respectively), increasing energy expenditure and reducing food intake [148,155-157]. During the feeding process glucose levels rise,

promoting the neuronal activity of POMC and the satiety signal [145].

A recent study revealed that POMC could also have an orexigenic effect by releasing β-endorphin, and by activating a μ opioid receptor, causing feeding induced by cannabinoid receptor 1 CB1R [158].

Agouti Related Peptide (AgRP)

It is an orexigenic hormone, it is formed by 132 amino acids with 11 cysteine residues that form disulfide bridges to carry out its function, [159] participates in energy homeostasis; In addition, it influences neuroendocrine regulation by activating the hypothalamic-pituitary-adrenal axis [160]. It is expressed in the brain, adrenal glands, testicles, lungs and kidneys [159,161]. This neuropeptide is activated by energy shortage, [162] within the arcuate nucleus; Its function is regulated by circulating neurons such as insulin, leptin, ghrelin, estrogens, glucocorticoids, glucagon-like peptide 1 and the YY peptide [163].

When activated, AgRP neurons block the activity of melanocortin receptors [164] to inhibit the catabolic actions of POMC, [161] it has also been seen to decrease when food occurs or during feeding, only a small amount being active; During this process, the AgRP signals from the arcuate nucleus to the paraventricular nucleus are inhibited when the food is presented and it is activated again when the food is removed again producing the "hunger" signal, so it is considered that these neuropeptides are modulated with sight and the smell [165,166]. In experimental animals it has been seen that overexpression of AgRP results in hyperphagia, hyperinsulinemia and obesity [167].

The mechanisms of the AgRP and POMC neuropeptides, involved in sleep were studied by Goldstein et al., In experimental animals, with sleep and food restriction, they found that by stimulating AgRP, wakefulness was promoted, while POMC activity contributed to reduce sleep in the face of food deprivation; Although these neuropeptides are not considered to influence sleep-wake status as primary factors, it was shown that energy homeostasis is dependent on sleep [168].

Neuropeptide Y (NPY)

Neuropeptide Y, is a pancreatic peptide composed of 36 amino acids with a linkage a tyrosine Y at the carboxyl end, this neuropeptide is derived from the pre-pro-NPY precursor, is distributed in the Central Nervous System (CNS) and Parasympathetic Nervous System (SNP)), [169] expressing itself in the hypothalamus, cerebral cortex and brainstem, [170,171] its synthesis is carried out in the arcuate nucleus, solitary tract nucleus, locus coeruleus and septohippocampal nucleus [172]. Of the receptors found only in humans, function Y1, Y2, Y4 and Y5 [173,174] have been seen, some of them related to feeding behavior such as Y1 and Y5. In addition, it is involved in energy homeostasis, surrounding rhythm, cognition and as a stress modulator, since it has been implicated in the regulation of the hypothalamus, pituitary, adrenal axis [175].

The role of NPY in food and sleep has already been mentioned in previous paragraphs [60,63-65,88-90,127,176].

It has been shown that NPY by inhibiting norepinephrine increases sleep, this mechanism is carried out due to the overexpression of NPY that decreases the level of mRNA of dopamine beta hydroxylase, in the Locus Coreulus, decreasing the levels of Noradrenaline [177].

Serotonin

Serotonin (5-hydroxytryptamine, 5-HT), is produced by tryptophan hydroxylase (TPH) that catalyze the formation of 1-5 hydroxytryptophan from an essential amino acid 1- tryptophan [178-181]. It is synthesized by cells of the gastrointestinal tract and only 5% in the CNS, [182] has 15 receptors of which only 5-HT3R, 5-HT4R and 5-HT7R work at the intestinal level [183].

It performs functions as a neurotransmitter and as a hormone in the intestinal vascular system [184]. Contributes to energy regulation and glucose balance through suppression of food [147] in addition to relating to depression, [185] sleep, [185,186] sex and temperature control [178]. Serotonin can activate primary afferent neurons as part of gastro intestinal motility and influence the transmission of information to the CNS, [187,188] specifically in the rafe nuclei, sending projections to the thalamus, striatum, nucleus accumbens, hippocampus and hypothalamus [181].

Serotonin in the regulation of appetite activates POMC neurons through the 5- HT2C receptor and the 5HT1 B receptor that is responsible for inhibiting NPY / AgRP neuropeptides contributing to the inhibition of food intake, [179] so decrease in serotonin levels could inhibit

the satiety signal and stimulate food intake, it has been seen that this signal varies according to the type of food that is being consumed in some cases favoring hedonic feeding and therefore obesity [180].

Norepinephrine

It is a catecholamine that acts as a hormone or neurotransmitter, is released in the locus coeruleus [188,189]. It is synthesized from tyrosine, in the synaptic neuron, where it is converted to dopamine due to the action of tyrosine hydroxylase, dopamine is transported to storage vesicles, where it is converted to norepinephrine by dopamine-β- hydroxylase [190] It is activated by G1-adrenergic, α2-adrenergic and β-adrenergic G protein-coupled receptors (GPCR) [188]. It is associated with memory, [191] food intake, energy homeostasis [192] and wakefulness [193].

In food intake, the expression of AgRP and NPY mRNA acts in the arcuate nucleus in response to glucose deprivation, [176] also inhibits POMC neurons, [194] due to binding to different receptors. In sleep, it is activated to promote wakefulness, [193] the elevation of norepinephrine causes the release of corticotropin-releasing hormone, which will stimulate the pituitary gland to release the adenocorticotropic hormone and the hypothalamus, pituitary, adrenal and therefore the production of cortisol, [195] which has been seen promotes vigilance, so low levels have been seen during NREM sleep while in REM they are almost imperceptible [193]. In the same way it has been seen that interaction with orexins can also induce wakefulness, when norepinephrine is stimulated optogenetically, the activity of orexins is induced by inducing wakefulness, so that the loss of signaling between norepinephrine and orexin receptors alter the sleep-wake cycle [188].

Dopamine (DA)

It is a catecholamine, synthesized in the synaptic neuron from L-Tyrosine and the tetrahydrobiopterin and oxygen cofactors [196]. It exerts its function through 5 receptors coupled to the G protein, grouped into two D1-like (D1 and D5) and D2-like (D2, D3 and D4) families [188]. Low levels of DA induce vasodilation and increase blood flow; high levels cause vasoconstriction and therefore a decrease in abdominal blood flow [182]. She has been involved in decision making, learning [197]. with intestinal homeostasis, gastric emptying, hedonic feeding [196], motivation and body movement coordination [186].

Its release in the ventral tegmental area and in the left black substance is modulated by glucose, increasing in hypoglycemia in the striatum and inhibiting its release in hyperglycemia in the middle brain [198] influencing the behavior of hedonic feeding since in hypoglycemia, preference has been seen in the consumption of foods high in sugar and fat [199,200].

Epinephrine

It is a catecholamine, it is produced in sympathetic nerve fibers and in chromaffin cells of the adrenal medulla, it is synthesized after the formation of dopamine in norepinephrine by the action of phenylethanolamine N-methyltransferase together with the cofactor S-adenosylmethionine [196]. The receptors under which it performs its function are primarily α 1 and β 2; It has similar functions to norepinephrine, including vasoconstriction with high levels and vasodilation at low levels, increasing blood flow, collaborating with glucose absorption.

Gamma-Aminobutyric Acid (GABA)

It is a CNS inhibitory neurotransmitter; it is expressed in the brain. They occur in the sublaterodorsal nucleus or subcoeruleus. It is synthesized by decarboxylation of glutamate mediated by glutamic acid decarboxylase, it is also produced by AgRP neurons, the release of GABA by this neuropeptide is essential for energy expenditure and food intake stimulated by ghrelin. It has been linked to the release of CRH, activation of HHA and the search for food [186,193,201-205].

It participates in the inhibition of POMC neurons due to their antagonistic actions in conjunction with neuropeptide Y in the ARC; while in sleep it has been seen that inhibition of GABA in the subcoeruleus nucleus reduces REM sleep and promotes wakefulness [193,201].

Conclusion

Sleep is an important factor for the development of obesity as seen in previous studies; the hormones involved in the regulation of appetite and sleep are usually modified in terms of secretion and production due to various internal and external factors that lead to having pernicious effects on health, sleep so far is not considered as a health problem in Mexico, however, chronic degenerative diseases that occupy the first places in morbidity and mortality. Lack of sleep and deregulation in the surrounding rhythms are considered among the main

factors for the development of these diseases that generate a greater demand for health care at all levels and an increase in health expenditures, research is essential future that clearly establishes the effects of some of the hormones in terms of weight gain.

Conflict of Interest: The authors declare no conflict of interest

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