Şahin, T, Tozcu, D. International Journal of Science Letters (IJSL). 2022. 4(1): 202-219.
https://doi.org/10.38058/ijsl.1053393

Review Article

Circadian rhythm and obesity

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Abstract

The earth rotates around its axis for 24 hours, this process creates physiological, biochemical, and behavioral rhythms in living things. These one-day periods are called the circadian rhythm. The circadian rhythm regulates human physiology and behavior by responding to environmental stimuli around the clock. The circadian system and sleep/wake phases are intertwined, and conditions such as sleep disorders, exposure to artificial light, jet lag, and shift work may cause disruptions in the circadian rhythm. Circadian rhythm; It is effective in gastrointestinal system physiology such as cell proliferation, electrolyte balance, digestion, absorption, motility. Disturbances in the circadian rhythm can cause imbalances in the intestinal flora, which can lead to disruptions in both the immune system and the absorption and digestion of macronutrients. In the human body, many endocrine factors are secreted in 24-hour periods and the amount of secretion reaches its peak at certain hours during the day. Disturbances in the circadian rhythm can cause many pathological conditions such as obesity and diabetes by causing disorders in the gastrointestinal system physiology, the secretion function of appetite hormones, and other endocrine factors secreted in 24 hours. Our aim in this review is to discuss the effects of circadian rhythm on gastrointestinal health and the relationship of hormones fluctuating with 24-hour circadian rhythm and obesity. The search was conducted in peer-reviewed journals PubMed, Web of Science, and Google Scholar. For this purpose, the keywords circadian rhythm and obesity were used together and research articles were included in this study.

Article History

Received 25.12.2021
Accepted 30.01.2022

Keywords

Circadian rhythm,
Gastrointestinal system,
Leptin,
Melatonin,
Obesity

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1. Introduction

Biological rhythms are a fundamental feature of life and shape many functions of living systems, from the molecular level to the organismal level (Mat et al., 2020). There are multiple time scales studied in nature that show rhythmic oscillations. Generally, they are divided into ultradian rhythm, infradian rhythm, circannual rhythm (Amanpour et al., 2021), and circadian rhythm. Short-period rhythms are expressed as ultradian rhythm, rhythms lasting weeks or more than 24 hours infradian rhythm, that repeat annually are expressed as circannual rhythm. (Stevenson, 2018; Amanpour et al., 2021).

In this review, the effects of circadian rhythm on gastrointestinal health and its relationship with obesity, hormones fluctuating with 24-hour circadian rhythm, and the effects of these hormones on obesity were discussed.

1.1. Circadian Rhythm

The term circadian rhythm comes from the circa (about) and dies (day). It is used to express the approximately 24-hour solstice. The circadian rhythm coordinates the internal timing of the organism with the outside world and is the main regulator of many physiological processes (Jaganath et al., 2017). The timing of the circadian rhythm is regulated by conditions such as light/dark, social/environmental, food/nutrition, temperature, chemical factors, mechanical stimuli. Light and the light-related sleep/wake cycle are the most effective circadian rhythm regulators (Akıncı and Orhan, 2016; Reid, 2019; Xie et al., 2019).

Circadian rhythm can be examined under two headings as central and peripheral clock. The central clock is located in the hypothalamus's suprachiasmatic nucleus (SCN). Many cells with molecular clocks in the body are regulated and protected by the main pacemaker located in the SCN (Serin and Acar Tek, 2019). The primary regulator of the SCN is the light stimulus. In mammals, light entering the eye first reaches the retina. (Wirz-Justice et al., 2021). The light is then received by special melanopsin-producing intrinsically photoreceptive retinal ganglion cells (ipRGC) in the eye. ipRGC transmits this information via the retinohypothalamic pathway to the SCN and other parts of the brain. The SCN transmits it to other organs of the body (Figure 1) (Logan and McClung, 2019). In this way, the organism distinguishes between day and night. Situations such as exposure to abnormal light, exposure to artificial light, and disruption of

sleep patterns may disrupt the relationship of the SCN with peripheral clocks and cause adverse health conditions such as psychological disorders, cancer, and metabolic diseases (Bedrosian and Nelson, 2017). Exposure to artificial light at night can also disrupt the secretion pattern of melatonin secreted from the pineal gland. Melatonin is responsible for circadian rhythm synchronization and has functions such as regulation of the sleep/wake cycle, modulation of pituitary and adrenal hormones, and regulation of the immune system. Therefore, the disorder in its release can cause many health problems (Vasey et al., 2021).

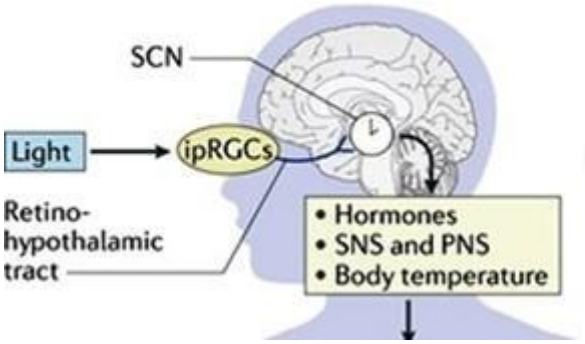

Figure 1. Light editing of the SCN (Logan & McClung, 2019)

Peripheral clocks are; direct the circadian expression of specific genes involved in many physiological functions (Serin and Acar Tek, 2019). Mammalian molecular clock; circadian locomotor output cycle includes a series of transcriptional-translational feedback loops including clock components such as hood (CLOCK), brain and muscle ARNT-like protein 1 (BMAL 1), Period (PER1-3), and cryptochrome (CRY1-2) (Stokes et al., 2017). In the primary feedback loop, CLOCK and BMAL1 form heterodimer complexes in the cytosol of SCN cells. This complex enters the nucleus and binds to regulatory elements of DNA containing E-Box. This binding activates the expression of the PER and CRY genes. PER and CRY then form a trimeric complex with casein kinaseIε/δ (CKI) and enter the nucleus. The PER-CRY complex acts on the CLOCK-BMAL1 complex and represses its transcriptions (Gul et al., 2021). In the second main transcriptional cycle, CLOCK and BMAL1, REV-ERBα and REV-ERBβ activate the transcription of nuclear receptors. The protein products compete with retinoic acid-associated, ligand unknown (orphan) receptors (RORα, RORβ, and RORγ) for binding sites (ROR-binding elements) in the BMAL1 gene. REV-ERB represses BMAL1 transcription; ROR increases BMAL1 activation. The third feedback loop includes D-box binding protein (DBP) binding to D-box elements and nuclear factor, interleukin-3-regulated protein (NFIL3/E4BP4). This cycle is regulated by CLOCK/BMAL1 and CRY1 (Figure 2) (Cox and Takahaski, 2019).

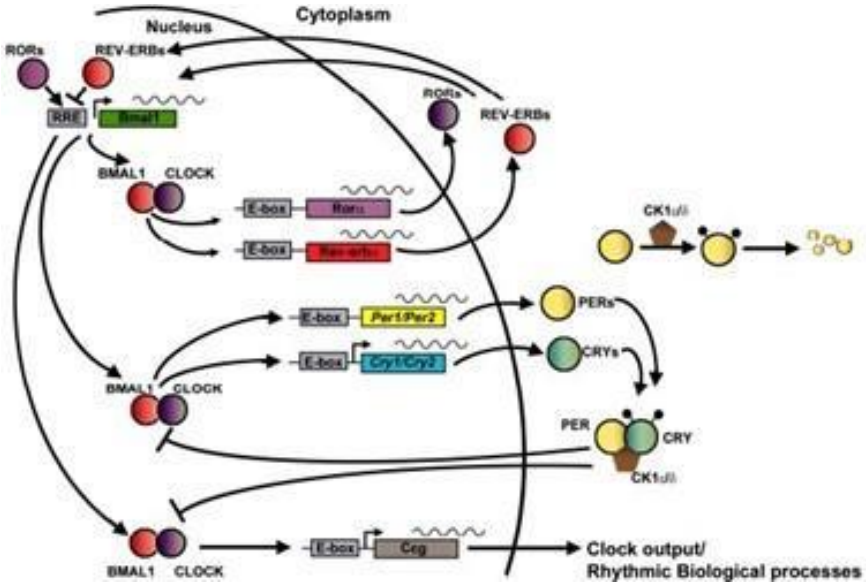

Figure 2. Mammalian circadian clock transcriptional and translational feedback network (Bhadra et al., 2017)

When the balance in the organism's body is observed, the biological/circadian clock from the molecular to the behavioral level must adapt to environmental changes. Conditions such as jet lag, shift work, and exposure to artificial light at night can cause misregulations in the circadian rhythm, disrupting the body balance and causing many adverse health problems. In addition, eating a high-fat diet and food intake at the wrong time can disrupt temporal physiological regulation (Figure 3) (Maury, 2019). The most studied and most common condition in the irregular circadian rhythm is the disruption of the sleep/wake cycle (Baron and Reid, 2014).

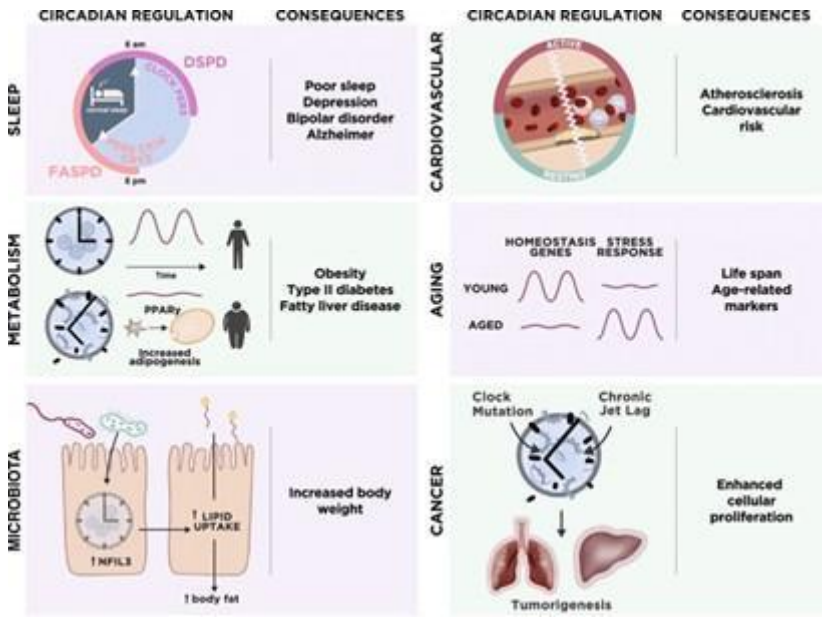

Figure 3. Results of circadian regulation and dysfunction in different physiological systems (FASPD: Familial advanced sleep phase disorder, DSPD: Advanced sleep phase disorder, NFIL3: Regulates lipid intake and body fat) (Rijo-Ferreira and Takahashi, 2019)

Another cause of disruptions in the circadian system is mutations or disorders in the circadian clock genes. This may result in a disturbance in human metabolism, as seen in Table 1.

1.2. Circadian Rhythm and Gastrointestinal System

Many mechanisms in the digestive system show circadian variations. For example, the circadian rhythm can maintain the intestinal barrier and regulate digestive physiology. In addition, depending on the circadian rhythm, the volume of saliva produced in the morning is more important than in the evening; gastric emptying in the stomach takes longer in the evening than in the morning (Codoñer-Franch and Gombert, 2018). In a study examining the effects of circadian rhythm on food intake; attenuation in feeding rhythm and hyperphagia were observed in BMAL1, Cry1–2, and Per2 mutant mice. Similar results were also obtained in mutant CLOCK mice (Page, 2021). According to experiments in mice in the regulation of gastrointestinal motility, it has been observed that the motility of organs such as the stomach, small intestine, the large intestine is closely related to the circadian rhythm. Mutations were made in the Per1/2h genes of the mice, resulting in changes in colonic muscle contraction. In addition, polymorphisms in components of circadian clock genes such as CLOCK and Per3 are associated with poor gastric motility in humans (Voigt et al., 2019). The gut is our

gastrointestinal tract organ, colonized by approximately 100 trillion microbes and mainly dominated by bacteria. The circadian rhythm is effective in regulating the intestinal microbiota. Jet lag etc. it has been shown by experiments on mice that circadian disruptions can cause dysbiosis in the intestinal microbiota due to various reasons. Circadian arrhythmic Per1 −/−; While it was observed that there were changes in the gut microbiota of mice with Per2 −/− pair disabled, it was observed that the gut microbiota also affected the circadian rhythm, and it was concluded that there was a bidirectional relationship between them (Rosselot et al., 2016).

Table 1. Metabolic consequences of circadian rhythm genes dysfunction, disruption, or gene mutations (Lee et al., 2015; Fatima and Rana, 2020)

Circadian Clock Genes	Conclusion
Stopping the BMAL1 function	Specific to liver tissue; elevated serum triglycerides, increased hepatic lipid, impaired circulating glucose clearance. Specific to smooth muscle tissue; impaired blood pressure rhythms. Specific to adipose tissue; changing feeding behavior and obese phenotype. Specific to the pancreas; altered insulin secretion. Specific to skeletal muscle; impaired glucose metabolism in muscles. In the whole body; increased free fatty acids and cholesterol, insulin resistance, glucose intolerance, weight gain, endothelial dysfunction. Impaired gluconeogenesis, adipocyte differentiation.
Stopping the CLOCK function	Slight weight gain
CLOCK mutation	Glucose intolerance. Disturbance in the size of pancreatic islets and defective proliferation. Vascular injury, endothelial dysfunction. Impaired circadian blood pressure.
CRY1 mutation	Diabetes
PER2 stop working	Deterioration in eating behavior, predisposition to obesity. Altered lipid profile, increased adipocyte differentiation. Decreased insulin clearance.
PER1/2/3 stop working	Predisposition to obesity.
Disruption of CRY1/2 functioning	Glucose intolerance
Rev-erbα/β dysfunction	Hepatic steatosis and dyslipidemia

It has also been observed that circadian rhythm dysfunction stimulates intestinal flora imbalance, independent of the nutrient source, and accordingly, it causes deterioration in the

immune system, and causes various pathological conditions (Cui et al., 2016). Circadian rhythms in innate adaptive immunity; it is effective by regulating events such as phagocytic activity, production of cytokines, number of circulating immune cells, and development of specific immune cell lines. For example, the circulating amounts of molecules that can respond to acute inflammatory action, such as lipopolysaccharides (LPS) in the outer membrane of gram-negative bacteria, or molecules such as Toll-like receptors TLR, increase at certain times of the day (Voigt et al., 2019).

The absorption and digestion of lipid, protein, carbohydrate macronutrients are under the control of the circadian clock to ensure simultaneous availability of nutrients in the gastrointestinal tract. Thus, enzymes involved in the digestion of these three crucial macromolecules are secreted in high amounts during food intake (Martchenko et al., 2020). Absorption of peptides transported across the intestinal barrier via the low-affinity lipid transporter 1 (PEPT1) is dependent on the sodium-proton exchanger (NHE3). The NHE3 gene, which is affected by the presence of food, contains E-Box and is under circadian control. Thus, it can be mentioned that there is a circadian rhythm in protein absorption. There is a lot of evidence that the circadian rhythm is also effective in regulating carbohydrate and lipid absorption. For example, absorption of monosaccharides from the intestinal lumen occurs with transporters such as sodium-dependent glucose transporters (SGLT1/2), enterocytes, glucose transporters 5 and 3 (GLUT5 and GLUT3), and the circadian clock is effective in these transporters (Voigt et al., 2019). In the absorption of lipids, three molecules named MTP, apo A-IV, and nocturnal were identified and it was observed that oscillators stimulated by both light and food affect the expression of these clock genes (Figure 4) (Hussain and Pan, 2015).

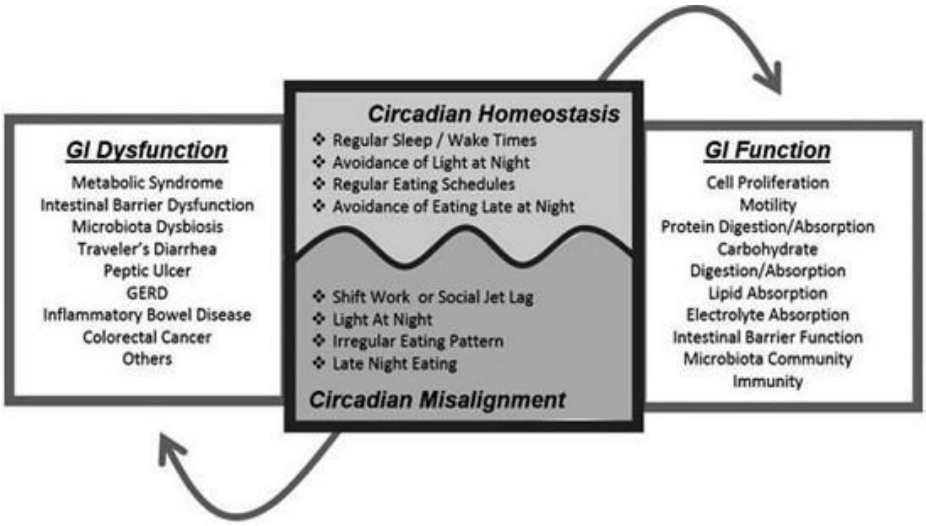

Figure 3. Circadian regulation of gastrointestinal function and dysfunction (Voigt et al., 2019) Various dysfunctions in the gastrointestinal tract may occur in the disruption of the circadian rhythm, which enables its biological functions to adapt to environmental conditions and predictable changes.

1.3. Circadian Rhythm and Obesity

According to the World Health Organization (WHO), obesity is defined as "abnormal or excessive fat accumulation that poses a health risk"; The World Obesity Federation, on the other hand, stated that obesity is "a chronic, recurrent progressive disease". In addition, epidemiological studies have shown that obesity can cause pathological conditions such as insulin resistance, cardiovascular disease, metabolic syndrome, and diabetes (Blüher, 2020). Disruptions in energy metabolism and circadian rhythm integrated with the environment can cause various pathological conditions, one of which is obesity (Sridhar and Sanjana, 2016). People with appropriate and inadequate sleep/wake cycles, such as shift workers, are more prone to conditions such as obesity. The most important accelerator of the disrupted circadian rhythm is exposure to light (LAN) at night, and light-sensing retinal ganglion cells reflect on SCN neurons, thus evoking a signal that leads to changes in Per1 and Per2 CLOCK gene expression (Noh, 2018). Imbalances in meal timing, such as shift work, or situations such as skipping meals can also lead to disruptions in biological rhythms. It has been reported that skipping breakfast, which is the first meal of the day, increases the risk of obesity more than skipping lunch or dinner (Orihara et al., 2020). In fact, in a study, it was observed that weight loss was higher when participants who consumed a single 2000 kcal meal in the morning were compared with those who consumed it in the evening (Halberg et al., 1995). In addition, studies

have shown that people exposed to artificial light at night have impaired secretion of plasma melatonin and leptin. In addition, it was observed that while plasma glucose levels were at high levels during the night, decreases in insulin secretion occurred. As a result, these studies have shown that exposure to light at night or working in shifts impairs insulin response (Pagano et al., 2017). Studies show that CLOCK gene expression in mouse adipocytes is decreased in the presence of diabetes and obesity. In addition, a decrease in adiponectin levels and a loss in the circadian rhythm of expression of adipokines were observed (Scott, 2015). Genes exhibiting circadian expression in visceral adipose tissue; CLOCK genes such as adiponectin, leptin, resistin, and visfatin. The functions of adiponectin and resistin in obese mice were greatly atrophied. In rats fed a high-fat diet, melatonin reduced plasma leptin levels in response to diet for three weeks. It has been observed that the circadian rhythm associated with this information regulates body weight by influencing hormone expression (Froy, 2010).

When the relationships between sleep-wake times and obesity depending on the circadian rhythm are investigated, it is generally thought that long sleep causes obesity, but according to these studies, it has been observed that subjects prone to obesity who claim to sleep longer spend more time in bed and sleep duration is short (Ogilvie and Patel, 2017). The relationship between short sleep duration and obesity in both adolescents and children is supported by the available literature. In addition, it has been observed that restriction during the sleep process changes orexigenic hormone functions, disrupts energy-glucose metabolism, and causes them to develop more unhealthy dietary behaviors (Hayes et al., 2018).

1.4. Hormones with Circadian Rhythm and Their Effects on Obesity

1.4.1. Melatonin

Melatonin, is a sleep regulator in humans and many living species, is secreted in a circadian rhythm and its secretion is regulated by the pineal gland (Morris et al., 2012). Melatonin levels rise at night and decrease during the day. About 2 hours after the production of melatonin, the deep sleep process begins. The circadian rhythm of melatonin is effective in individuals with and without visual impairment (Zisapel, 2018). Exposure to light at night can reduce melatonin levels and disrupt many physiological processes. Melatonin, which has effects on suppressing ultraviolet (UV) damage in skin cells, wound healing, hair growth, and anticancer, can also be taken orally to induce sleep (Lyons et al., 2019). In addition, the circadian amplitude of

melatonin may decrease with age (Goswami et al., 2020). Circadian timing, which has positive effects on physical and mental health; melatonin is directly affected by melatonin receptor agonists and light (Emens and Burgess, 2015). It has been shown to enhance the circadian rhythm in newborns through the transfer of melatonin with colostrum. Therefore, the inability of the newborn to be fed with breast milk causes disruptions in the circadian rhythm. In this case, disruptions occur in the physiological processes of the baby, who cannot reach melatonin sufficiently. e.g., excessive weight gain is observed independent of caloric intake. In addition, it has been shown that the secretion rhythm of melatonin is impaired in obese mothers, and similar situations have been found in the children of these mothers (Ivanov et al., 2020). In addition, melatonin receptor dysfunctions (MT1 and MT2 receptors) have been associated with diabetes (Gamble et al., 2014).

1.4.2. Leptin

Leptin is a satiety hormone produced by adipocytes and circulated in proportion to body fat (Patton and Mistlberger, 2013). Leptin has endocrine and paracrine effects (Berger and Polotsky, 2018). After leptin is secreted from adipocytes, it crosses the blood-brain barrier to the brain and binds to its receptor LepR. In addition, leptin is encoded by the obese (ob) gene (Audira et al., 2018).

The circadian rhythm has an important place in the leptin cycle. BMAL1 and CLOCK heterodimers regulate CCAAT-enhancing protein alpha (C/EBPα) activity in adipose tissue. C/EBPα is the most potent transcriptional activator for leptin, and this regulation indicates that the heterodimers of BMAL1 and CLOCK are directly involved in leptin modulation. In addition, this regulation rhythmically enhances the leptin response of the SCN clock Arcuate Core (ARC) neurons in the Central Nervous System (Kettner et al., 2015). While it is low in the early morning, it increases during the day and is at its highest level late at night. Those that affect leptin levels for 24 hours are; sleep loss or prolonged sleep, circadian phase, excessive food intake, or calorie restriction (Nguyen and Wright Jr, 2010). In animal studies, sleep deprivation caused disturbances in leptin secretion, and sleep-deprived rats showed lower leptin levels and increased energy expenditure (Olson et al., 2016). In addition, slow-wave sleep (SWS) increased while REM sleep decreased in leptin-fused rodents. In another study conducted on humans, 4 hours of sleep restriction showed a 23-24% increase in appetite and hunger, and an 18% decrease in leptin hormone (Kim et al., 2015). As a result, chronic or acute

sleep deprivation can cause an increase in food intake and weight, which can lead to obesity, diabetes, etc. can cause pathological conditions.

1.4.3. Ghrelin

Ghrelin, an orexigenic hormone, stimulates the secretion of adrenocorticotropic hormone (ACTH) and growth hormone, thus increasing food intake and appetite. It also increases gastric acid secretion and intestinal motility, affects energy expenditure, contributes to the hedonic aspects of food, and lowers arterial blood pressure (Gray et al., 2019). Ghrelin is secreted by endocrine cells of oxyntic glands in the fundus of the stomach; it is secreted in small amounts by the duodenum, jejunum, stomach body, as well as by the pituitary gland, lungs, and urogenital organs. To produce active ghrelin, the enzyme Grelin-O Acyltransferase octanylates the inactive form then attaches an acyl side chain to the serine residue at position 3. This chain is critical in the gastric emptying and appetite-enhancing functions of ghrelin (Makris et al., 2017).

While plasma ghrelin levels vary according to feeding times, they are highest during the day and lowest at night. Acting on the circadian system, ghrelin is a potential feedback signal for the SCN. It has also been discovered that ghrelin secretion is regulated in Per1 and Per2 in the stomach. Thus, it has been reported that ghrelin can regulate the peripheral circadian rhythm (Wang et al., 2018). Ghrelin-secreting cells are Food Driven Oscillators (FEO) because in mice oxyntic cells express circadian cycles of CLOCK gene expression associated with mealtime (Mistlberger, 2020). In nocturnal animals fed only during the day, there is a large increase in premeal circulating ghrelin (Challet, 2015). In a study conducted to reveal the relationship between sleep and appetite, the difference between 4 hours of sleep in 2 nights and then 10 hours of sleep in 2 nights was examined. While leptin decreased by 18% compared to long sleep during short sleep, it was observed that ghrelin increased by 28% in short sleep. Appetite for high-carbohydrate foods increased after a short nap, with a 32% increase (Leproult and Van Cauter, 2010).

1.4.4. Insulin

Insulin is secreted by β cells in pancreatic islets. It responds to levels of circulating nutrients such as free fatty acids, amino acids, and glucose. If the circulating level of insulin is insufficient

to stimulate glucose uptake from the blood, protein and fat stores are used for energy production (Kolb et al., 2020). Insulin signaling begins with its binding to the cell surface insulin receptor (IR), a tyrosine kinase, and with MEK/ERK, AKT/PI3K/mTOR, NOX4 signaling pathways, lipolysis, gluconeogenesis, lipid/protein/glucose synthesis, and glucose uptake are effective in cell proliferation (Posner, 2017; Kolb et al., 2020). While it is thought that there is a connection between the increasing obesity problem in the world and insulin resistance, the underlying causes of this connection have been investigated and it has been observed that melatonin is secreted less in insulin-resistant individuals (Otamas et al., 2020). In studies with rodents, melatonin receptors (MT1 and MT2) and melatonin interactions on the beta-cell surface have been shown to inhibit insulin secretion from beta cells (Onaolapo and Onaolapo, 2018).

According to the experiments, reasons such as sleep restriction, circadian disruption, behavioral and environmental evening causes problems in insulin sensitivity (Mason et al., 2020). According to an experiment conducted with volunteers over 28 weeks, insulin and glucose levels increased independently of the time after a meal, while their levels decreased during sleep. They also found that circadian disruption may be effective in insulin resistance, which may cause weight gain and obesity (Mesarwi et al., 2013).

1.4.5. Adiponectin

Adiponectin found in adipose tissue and encoded by the Adipo Q gene has 224 amino acids and weights 28 kDa. Adiponectin, which is effective in the metabolism of carbohydrates and lipids, especially in muscle and liver, as well as energy homeostasis; has also been found to have anti-atherogenic and anti-inflammatory effects. Adiponectin also; It has also been detected in lymphocytes, adrenal glands, osteoblasts, skeletal muscle, cardiomyocytes, testis, ovary, and placenta (Nguyen, 2020). Adiponectin, which has two receptors as AdipoR1 and AdipoR2, plays a crucial role in reducing pathological conditions such as obesity-related type 2 diabetes/insulin resistance and cardiovascular diseases. While adiponectin is positively associated with insulin sensitivity, a decrease in serum levels of adiponectin is observed in obesity (Achari and Jain, 2017; Straub and Scherer, 2019).

Adiponectin is one of the fat-derived endocrine factors (i.e. adipokine) and has a time-of-day rhythm. This rhythm is also associated with increased insulin secretion later in the day (Gamble et al., 2014). In a study with experimental animals, although adiponectin showed

minimum expression around 10:00 and 11:00 in the morning, high adiponectin expression was observed in humans at the same hours. This showed that circadian secretion of adiponectin occurs in opposite phases between night-active mice and day-active humans (Gómez-Abellán et al., 2010). Adiponectin expression is regulated by the circadian clock and its co-activator PGC1α and circadian expression of the transcription factor PPARγ (Barnea et al., 2015). In a study, adipose tissue was taken from obese women, and AdipoQ, AdipoR1, and AdipoR2 genes were examined. According to the results of this experiment, it was concluded that these three genes exhibited 24-hour rhythmicity and adiponectin expression was regulated at the mRNA level and time-dependently (Gómez-Abellán et al., 2010; Barnea et al., 2015). Apart from nutrient-sensitive hormones that have a direct effect on obesity and appetite, many endocrine factors respond to environmental conditions and are secreted over 24 hours. At certain times of the day, the secretion of these endocrine factors reaches its peak and becomes effective on the organism and metabolism (Table 2).

2. Conclusion

The circadian rhythm, which regulates many physiological functions of the organism, is particularly affected by the light/dark cycle, and therefore by the sleep/wake phases. According to the results of the literature review; conditions such as exposure to artificial light at night, social jet lag, shift work, and eating late can lead to circadian disruptions, thus deterioration in gastrointestinal functions such as absorption, digestion, motility, and this may result in various pathological conditions. Although obesity is known as an excessive amount of fat accumulation in the body, it can bring conditions such as metabolic syndrome, insulin resistance, diabetes, and cardiovascular diseases. Recently, it has been thought that circadian rhythm and sleep/wake processes may be associated with obesity, and many studies have been conducted. Although it is generally thought that long sleep periods play a role in the process leading to obesity, studies have shown that short sleep (less than 6 hours of sleep) rather than long sleep may be more effective on obesity. The shortening of the sleep period resulted in spending more time on eating, more tendency to carbohydrate foods, and the appetite hormones secreted with the circadian rhythm and the secretion of the melatonin hormone, which plays a very important role in the circadian rhythm, causing disorders in the secretion, increasing the appetite and inviting obesity. The circadian rhythm is highly effective on obesity. Although it is not known for certain whether circadian disruption causes functional disorders in the gastrointestinal system of the individual or causes disorders in the secretion of endocrine factors secreted by the

circadian rhythm, it should be accepted that it is one of the important underlying causes of obesity and further research is required considering the contributions it will provide to the literature.

Table 2. Other endocrine factors known to be released over 24 hours in humans (Gamble et al., 2014)

Hormones	Rhythm Based on Time of Day	Peak Point	Function in the Body
Cortisol	Yes	07.00-08.00 a.m.	Stress response İmmune response Glucose and protein homeostasis (Thau et al., 2021)
GH	Yes	increased secretion at night	Growth, Cell division and regeneration Regulation of metabolism Effective in Immunity, Reproduction, Cardiovascular System (Lin et al., 2018)
Testosterone	Yes	07.00 a.m.	Male reproductive organs development and hair growth Increasing bone, muscle mass (Banihani, 2018)
TSH	Yes	01.00-02.00 a.m.	Regulates the work of the thyroid gland, provides the secretion of Thyroxine and Triiodothyronine
PRL	Yes	02.00 a.m. (amplitude is greater in females)	Milk production and development of the mammary glands Maintaining homeostasis (Al-Chalabi et al., 2020)
T_3	Yes	02.30-03.30 a.m.	Increases basal metabolic rate Regulates growth (Mullur et al., 2014)
Vasopressin	Yes	Midnight	Body water balance Blood pressure regulation (Bankir et al., 2017)
FGF21	Yes	05.00-08.00 a.m.	Regulates simple sugar intake and tendency to sweet foods (Tezze et al., 2019)
RAAS	Yes	Early morning	Regulates blood volume and blood pressure (Ames et al., 2019)

*GH, growth hormone; TSH, thyroid-stimulating hormone; PRL, prolactin; T3, triiodothyronine; RAAS, the renin-angiotensin-aldosterone system; FGF21, fibroblast growth factor 21

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