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Review

Melatonin - leptin interaction and obesity-related genes

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Abstract: Most living organisms have circadian clocks which maintain rhythm in internal cycles of behavior, physiology, and metabolism, allowing them to anticipate the earth's 24-hour rotation. In mammals, circadian integration of metabolic systems optimizes energy gathering and usage across the light and dark cycles. Disruption of circadian rhythms may lead to metabolic dysfunctions such as obesity and obesity-related disorders. The molecular and hormonal mechanism behind obesity is mostly related to mRNA expressions in hypothalamus, and leptin, and melatonin hormone levels. In obesity and related disorders, the chronobiotic hormone melatonin regulates physiological functions such as energy metabolism, body fat, and reproduction by cross-interacting with leptin. Leptin signals satiety by inhibiting Neuropeptide Y/Agouti-Related Peptide (NPY/AgRP genes in hypothalamus and exerts its effects on food intake, body weight, and the reproductive system. In this review, the molecular and hormonal mechanisms behind obesity were discussed.

Özet: Çoğu canlı organizmanın, davranış, fizyoloji ve metabolizmanın iç döngülerinde ritmi koruyan sirkadiyen saatleri vardır ve bu da organizmaların dünyanın 24 saatlik dönüşünü tahmin etmelerine olanak tanır. Memelilerde, metabolik sistemlerin sirkadiyen entegrasyonu, ışık ve karanlık döngüleri boyunca enerji toplanmasını ve kullanımını optimize eder. Sirkadiyen ritimlerin bozulması obezite ve obeziteye bağlı bozukluklar gibi metabolik işlev bozukluklarına yol açabilir. Obezitenin arkasındaki moleküler ve hormonal mekanizma çoğunlukla hipotalamustaki mRNA ifadeleri ve leptin ve melatonin hormonlarının seviyeleriyle ilişkilidir. Obezite ve ilgili bozukluklarda kronobiyotik bir hormon olan melatonin, leptin ile çapraz etkileşime girerek enerji metabolizması, vücut yağı ve üreme gibi fizyolojik işlevleri düzenler. Leptin hormonu hipotalamustaki Nöropeptid Y/Agouti İlgili Peptid (NPY/AgRP) genlerini inhibe ederek tokluk sinyali verir ve besin alımı, vücut ağırlığı ve üreme sistemi üzerinde etkilerini gösterir. Bu derlemede obezitenin arkasındaki moleküler ve hormonal mekanizmalar tartışılmıştır.

Introduction

Obesity is increasingly recognized as a serious, worldwide public health concern. Even though it is preventable, due to comorbid diseases of obesity such as cardiovascular, reproductive, and endocrine system problems, obesity has become one of the tough disorders in the society (World Health Organization [WHO] 2021). It is an uncontrolled increase in body weight which can be defined as a disorder resulting from a disruption in energy metabolism (Jais & Brüning 2017). Excessive fat accumulation in white adipose tissue or some organs due to an imbalance in energy homeostasis may lead to the development of obesity. Energy homeostasis is managed in the hypothalamic region by a sophisticated network of orexigenic and anorexigenic signals (Kalra *et al.* 1999). There is ample evidence on that suprachiasmatic nucleus (SCN), arcuate nucleus (ARC), pineal gland and white adipose tissues have important roles in organizing the energy balance of the body (Morgan *et al.* 2003). This complex network system could be easily corrupted by environmental factors (i.e. feeding time) if they last a prolonged time. In this context, this review aims to briefly discuss the role of melatonin and leptin in the development of obesity and changes in obesity-related gene expression.

Leptin and Obesity, Obesity- Related Genes

As in humans, many animals regulate their body weight, reproduction, and energy gain/expenditure according to various environmental factors (Reiter 1974, Stetson *et al.* 1975). Sustaining vitality depends on the effective use of essential nutrients and energy storage. In this sense, the homeostasis between gained and

expended energy is critical for all organisms (Galgani *et al.* 2010). Excessive calorie intake and a lack of exercise have been used to explain the dramatic rise in obesity, but this only serves to highlight the need for a new look at the mechanisms underlying how obesity develops and shapes metabolism. Studies have found a connection between obesity and a 24-hour lifestyle and the sleep-wake cycle (Bray & Young 2012, Shochat 2012). At the heart of this link between sleep and obesity is the endogenous rhythm, also known as the circadian rhythm, which is regulated by both genetic and environmental factors. This rhythm controls the expression and/or activity of the hormones and enzymes involved in metabolism. But there is increasing evidence showing that eating habits, mealtimes, and specific nutrients also have an impact on metabolism by affecting circadian clocks (Jamshed *et al.* 2019, Charlot *et al.* 2021). Therefore, metabolic disorders can be caused by circadian rhythm disruptions.

Obesity is a central nervous system disease occurring due to several dysfunctions between hormonal and neurological mechanisms (O'Brien *et al.* 2017). There is clear evidence showing that the circadian clock, controlled by the SCN which is located in the hypothalamus, synchronizes physiological functions to optimize metabolic efficiency. Even though SCN serves as the body's pacemaker, peripheral clocks are also a part of the mammalian circadian system. These coordinated peripheral clocks in other organs send signals to the SCN, the body's main clock (Fig. 1). To induce optimal energy homeostasis, both central and peripheral clocks need to be synchronized. Otherwise, disruption in the circadian clock may result in alterations in gene expression and hormone levels.

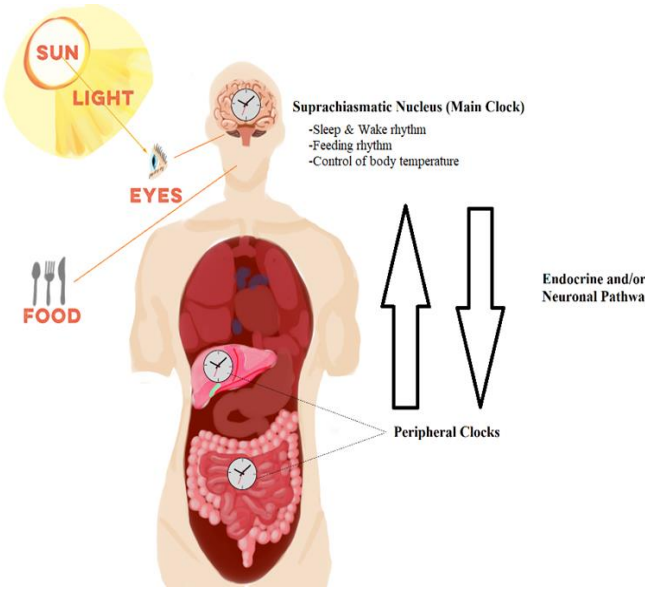

Fig. 1. Relationship between main clock and peripheral clocks. There is mutual communication between the SCN and the peripheral clocks. Light is the most important initiating signal of this system.

Through molecular studies, it has been established that all vertebrate cells and tissues display a circadian rhythm. The liver, intestines, and adipose tissue are just a few peripheral tissues of mammals that exhibit independent circadian oscillations (Mohawk *et al.* 2012). The analysis of the gene expression profile in mammals revealed that 3% to 20% of the genes displayed 24-hour expression, and the majority of these genes were involved in metabolic processes. Although organs in the periphery exhibit consistency in their circadian rhythms their functions can be affected if circadian rhythms within or between tissues are disturbed. Differentiation in temporal gene expression has been found to be important in organs involved in glucose and lipid metabolism, such as skeletal muscle, liver, heart, and adipose tissue. The liver and white and brown adipose (fat) tissues have also been found to contain a large number of nuclear receptors with rhythmic activity. Thus, it is possible to figure out the connection between nuclear receptors and clock genes, which regulate energy flow in response to altering physiological needs during the light/dark cycle in metabolism. In this way, the circadian rhythm of metabolic gene expression ensures the best possible exchange between the anabolic and catabolic processes brought on by feeding and fasting periods. For instance, nutrition can maximize the levels of enzymes in adipose tissue. However, it was discovered that the mouse liver experiences a peak in the processes of glycolysis, gluconeogenesis, and fatty acid metabolism overnight. Changes in the circadian rhythms of peripheral *Clock* genes have been linked to an increase in body weight, abnormalities in glucose homeostasis, and blood pressure regulation, all of which contribute to the development of metabolic syndrome. These adjustments may be the result of behavioral or environmental changes, such as a high-fat diet interfering with circadian rhythms.

Circadian Rhythm and Metabolism

Many hormones, including insulin, glucagon, adiponectin, corticosterone, leptin, and ghrelin, have been shown to exhibit circadian release. These hormones play important roles in metabolism. It is well known that leptin plays a significant role in in the hypothalamus and, when released from adipocytes under physiological conditions, suppresses appetite and accelerates metabolism. The circadian rhythm of leptin was abolished in hamsters as a result of SCN lesion, implying that the circadian clock regulates leptin production (Karakaş & Gündüz 2006). Additionally, unlike healthy animals, rats with SCN-lesions did not increase the level of free fatty acids in plasma after intraperitoneal administration of leptin, indicating that SCN may also play a role in leptin (Li *et al.* 2012). The circadian clock has been implicated in the regulation of metabolism and energy balance in peripheral tissues, in addition to its effects on the endocrine system. The circadian clock conveys this function by mediating the production and/or activity of some metabolic enzymes (glycogen phosphorylase, cytochrome oxidase, lactate dehydrogenase, acetyl-CoA carboxylase, malic enzyme, fatty acid synthase, glucose-6-phosphate dehydrogenase) and transport systems involved in the metabolism of

cholesterol, amino acids, drugs, toxins, glycogen, and glucose and in the citric acid cycle (Marcheva *et al.* 2013).

The Effect of Nutrition on Circadian Rhythm

Feeding, one of the strong major environmental signals, is known to impact circadian oscillators. Karakaş *et al.* (2006) demonstrated that locomotor activity of Mongolian gerbils was advanced by the food restriction phase. The neuronal link between the pineal gland and the SCN may be the cause of the mechanism underlying this effect. Food restriction phase advances with the release of rhythmic melatonin hormone by the pineal gland (McArthur *et al.* 1991, Selmaoui *et al.* 2001, Challet *et al.* 2003). Another study revealed that rats fed a high-fat diet had alterations in circadian rhythm. The amplitude of daily pineal melatonin rhythm was shown to decrease in obese rats (Cano *et al.* 2008). In obese Sprague-Dawley rats administration of melatonin reduced body weight and leptin level. However, body weight and food efficiency increased in obese pinealectomized animals. When these animals were treated with melatonin, body weight, and food efficiency were not different from the sham-operated control group (Prunet-Marcassus *et al.* 2003). Likewise, in one of the experiments reported in Gündüz & Karakaş (2001), daily 4-hour melatonin infusions between 17:00-21:00 inhibited body weight growth in pinealectomized juvenile Siberian hamsters. A recent study also underlined that misalignment of feeding rhythm induces disruption in the circadian clock and obesity. Restricted feeding to active phases of the daily rhythm (night time for rodents) resulted in increased energy expenditure in mice fed high fat diets (Hepler *et al.* 2022). These studies demonstrate the role of melatonin in body weight gain. Given that overeating or dietary content affects circadian rhythmicity and that feeding is a significant environmental signal, it appears that obesity is one of the diseases connected to circadian rhythms.

The relationship between appetite regulation and food intake is crucial to understanding the causes of obesity. Leptin is one of the major elements in this mechanism and is synthesized mainly from adipose tissue into circulation which binds its receptors in hypothalamus (Schwartz *et al.* 1996). This hormone, which is derived from adipocytes, regulates energy metabolism as well as many other processes, including feeding and reproduction (Mercer *et al.* 1996, Meli *et al.* 2004).

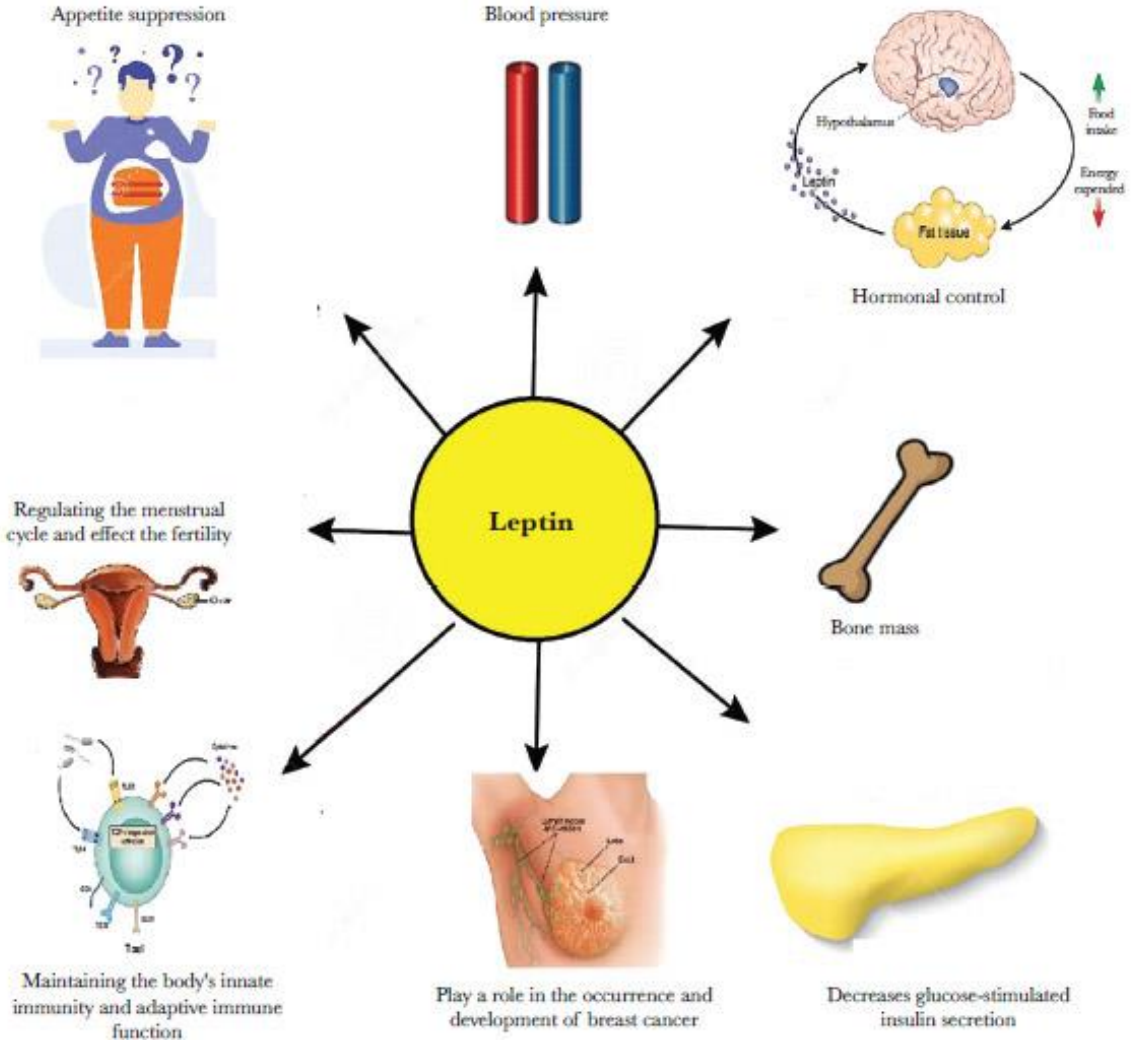

Fig. 2. Effects of leptin on different tissues (Al-Hussaniy *et al.* 2021).

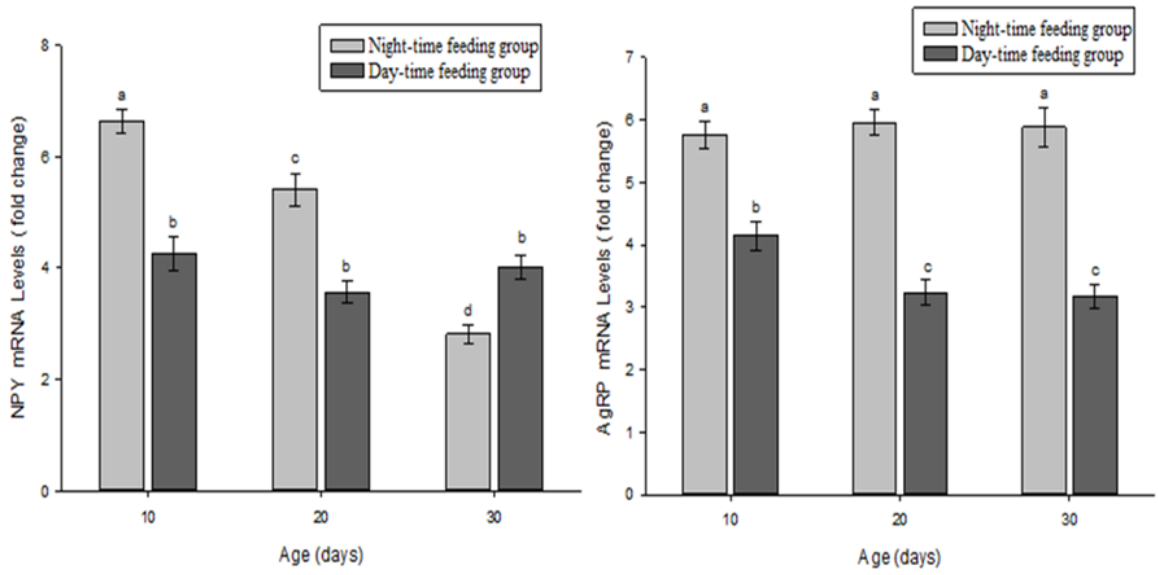

Fig. 3. NPY and AgRP mRNA expressions of offspring of Syrian hamsters, *Mesocricetus auratus* (Waterhouse 1838) relative to the *ad libitum* group. Different letters indicate statistical significance.

Leptin inhibits Neuropeptide Y (NPY) and Agouti-Related Peptides (AgRP) via its receptors in the ARC, which are responsible for regulating food intake and energy balance (Schwartz *et al.* 2000). Because NPY and AgRP co-express in hypothalamus, a recent study found that NPY-originated AgRP neurons control feeding initiation via Npy1r signaling, but Npy2r signaling controls locomotion and energy expenditure (Qi *et al.* 2022). Another study showed that the AgRP neurons in mice are inhibited at the start of the dark phase, which prevents them from eating, but that they are stimulated at the start of the light phase, when the mice are full (Krashes *et al.* 2011). The complementary characteristics of NPY and AgRP include the fact that NPY temporarily prolongs hunger after gaining access to food while AgRP controls feeding over a longer period of time. Additionally, feeding was eliminated when NPY was deleted, but not AgRP or GABA, leading researchers to hypothesize that NPY plays a special role in sustaining hunger in the interval between food finding and consumption (Chen *et al.* 2019).

Epidemiological studies on humans and animals have shown that nutrition is essential for the metabolic control of energy balance from very early development (McMillen *et al.* 2008, Varela *et al.* 2021). A food limitation during pregnancy and lactation may alter the offspring's metabolic processes permanently and alter the likelihood of obesity in adulthood (McMillen *et al.* 2005, Martin-Gronert & Ozanne 2006). In our recent study (İnan & Gündüz 2024), we showed how an important maternal factor such as nutrition affects the gene expression of hypothalamic neuropeptides NPY/AgRP in the brains of offspring and how this changes from the early stages of development (up to day 30) (Fig. 3). The findings indicate that dietary modifications during the very early stages of development have a considerable impact on the expression of NPY/AgRP mRNA in offspring. The variation in expression of neuropeptide genes during and after lactation is notable. Our research shows that feeding the young at different times of the day has the biggest impact during the lactation period, since this was the moment when both NPY/AgRP protein levels and mRNA expression increased. It is well recognized that a mother's poor eating schedule or undernutrition increases the offspring's risk of metabolic problems. Our discoveries could change the course of metabolic disease, provide a new understanding of energy metabolism, and pinpoint new areas for early disease prevention and therapy through nutritional strategies in the early years of life. The neural development of the offspring is influenced by maternal variables during pregnancy, which may also control the programming of dietary neuropeptide gene expression throughout life.

In 1953, Kennedy developed the idea that circulatory impulses produced in proportion to body fat storage regulate appetite and energy expenditure in a coordinated manner to balance body weight (Kennedy 1953). The existence of such circulatory impulses was demonstrated by Coleman in his landmark research on parabiosis in 1973. The obesity gene (ob) mutation prevents the formation of a circulating anorexic factor, as demonstrated by Coleman's tests that compared the circulatory systems of two strains of highly obese mice (ob/ob and db/db) with wild-type animals and with one another. However, he discovered that the diabetes gene (db) mutation reduces the responsiveness to this factor. As a result, it was discovered that the db/db mutant mouse produced excessive satiety factor but could not respond to it due to a malfunctioning receptor, while the ob/ob mutant recognized and responded to same satiety factor but failed to produce it. The Ob gene was cloned in late 1994 and revealed to encode a 16 kDa protein known as leptin or the OB protein, which is produced by adipose tissue and released into the bloodstream (Zhang *et al.* 1994). When leptin deficit is corrected in ob/ob mice, food

intake is significantly decreased, and the obesity condition returns to normal. Therefore, obesity in mice is caused by both leptin resistance (in db/db mice) and leptin insufficiency (in ob/ob animals). Consequently, leptin functions as a crucial negative feedback signal for the regular regulation of food consumption and body weight (Frühbeck *et al.* 1998, Coleman 2010).

The behavior and physiology of experimental animals have been found to be significantly affected by restricting food intake at specific times of the day (limiting the amount and duration of meals without reducing energy intake). It was discovered that two to four hours prior to a meal, experimental animals displayed food expectancy behaviors such as increased locomotor activity, body temperature, corticosterone release, gastrointestinal motility, and activity of digestive enzymes (Nelson & Halberg 1986). All of these data are said to be indicators of the biological clock. Many physiological processes controlled by the SCN are observed to change with the restriction of daytime feeding, and it has been observed that restricted nutrition has an impact on SCN (Tacad *et al.* 2022). In animals with SCN lesions and mutant mice, it has been reported that limited feeding affects circadian rhythm independently of light (Froy 2007). In addition, studies have shown that limited nutrition affects circadian oscillators in peripheral tissues such as liver, kidney, heart, and pancreas without affecting the rhythm-regulating mechanism in SCN (Oosterman *et al.* 2015). For this reason, it was thought that the regulation of *Clock* oscillators in peripheral tissues with nutrition may play a direct role in the coordination of metabolic oscillations.

Energy restriction or reducing the amount of energy in the diet without resulting in malnutrition has been found to increase rodents' life spans by up to 50% (Barger *et al.* 2003). In addition to increasing life expectancy, energy restriction also delayed the onset of age-related pathophysiological changes such as cancer, diabetes, kidney diseases, and cataracts (Weindruch & Sohal 1997). The mechanism of these effects of reducing energy consumption on aging and lifespan is still not fully understood. The synchronization of peripheral oscillators, however, is believed to be directly mediated by the time of eating or by synchronization of the SCN, which sends humoral or neural signals to peripheral tissues, during the restriction of nutrition and energy intake.

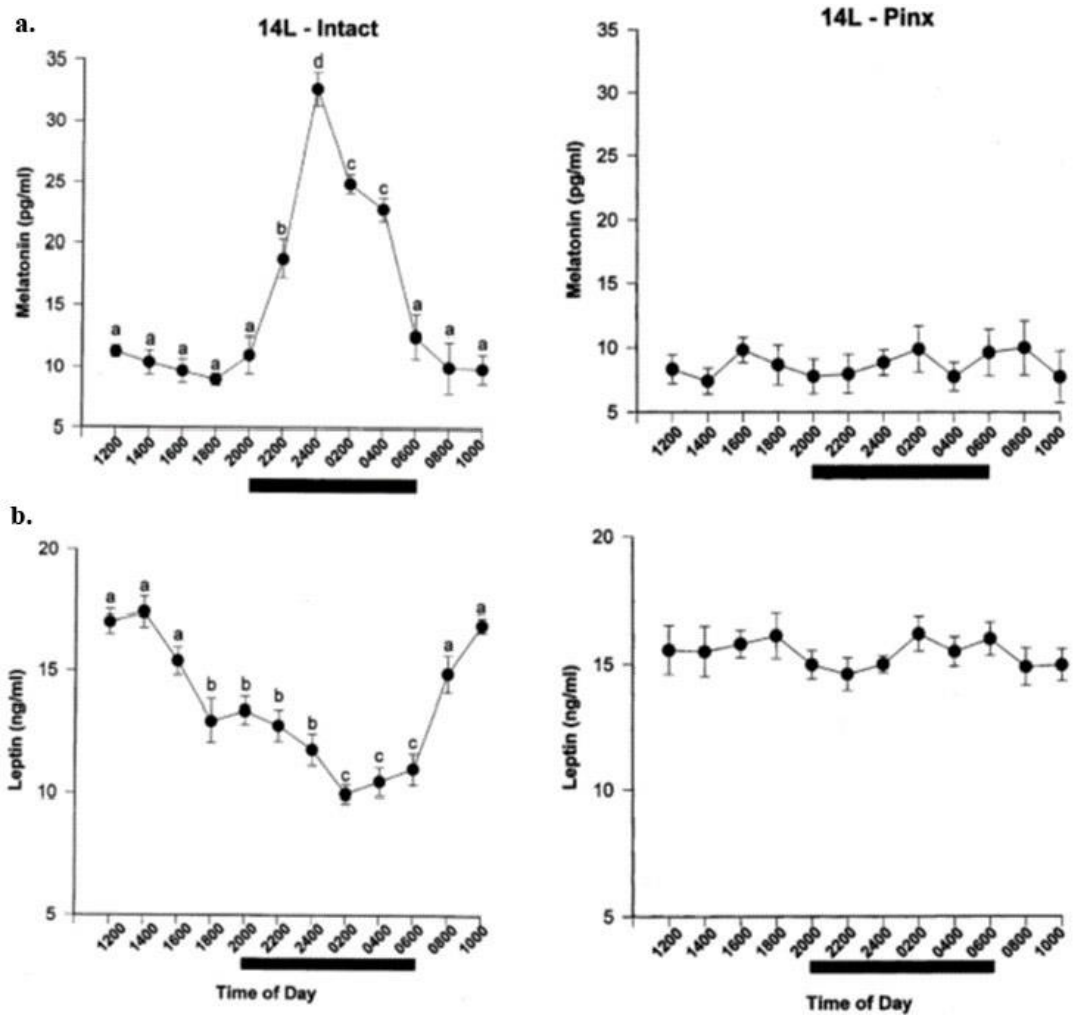

Fig. 4. Twenty-four-hour serum melatonin and leptin levels in intact and pinealectomized hamsters in 14L photoperiod. **a.** Melatonin, **b.** leptin (Gündüz 2002).

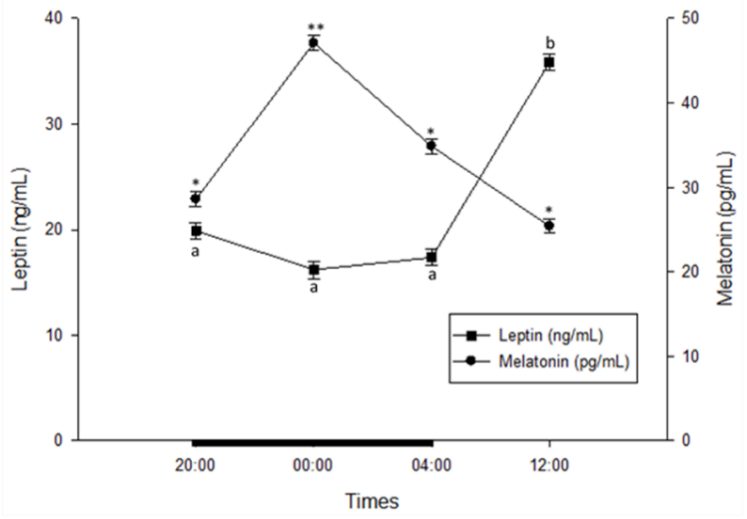

Fig. 5. Leptin and melatonin values in male Syrian hamsters (Balkan & Gündüz 2023).

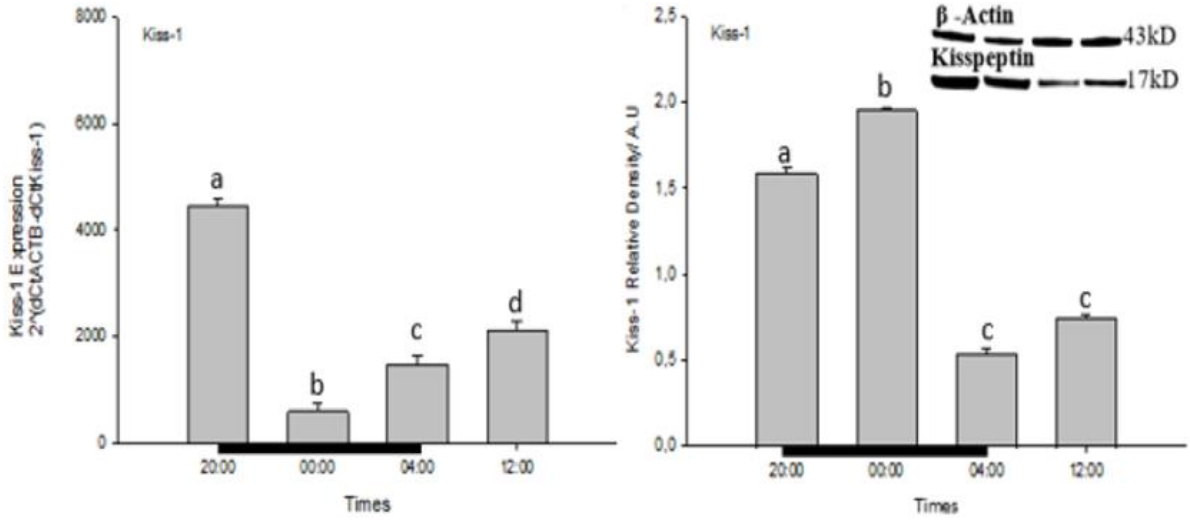

Fig. 6. Quantification of mRNA expression and relative protein density changes at different times of day (20:00, 00:00, 04:00, and 12:00). Different letters indicate significant levels (Balkan & Gündüz 2023).

The circadian rhythm of genes involved in controlling energy homeostasis and feeding regulation are intrinsically linked. In our most recent study, nighttime and daytime feeding restrictions reduced the body weight of Syrian hamster pups while increasing NPY/AgRP mRNA expression (Fig. 3) (İnan & Gündüz 2024). To reduce energy requirement in fasting conditions NPY reduces body weight and bone formation (Lim *et al.* 2006, Coupé *et al.* 2009). Although leptin regulate the expression of the NPY/AgRP gene, melatonin also plays a crucial part in the control of food intake. As shown by Gündüz & Hasanoğlu (2016), melatonin increased the expression of NPY/AgRP genes in the hypothalamic region of the brain, but leptin decreased the levels of these neurotransmitters. Moreover, pinealectomy increased leptin hormone levels and decreased AgRP gene expression. Melatonin is therefore a highly effective regulator of feeding-related gene expression (Gündüz & Hasanoğlu 2016).

Leptin and Melatonin Interaction (Obesity & Reproduction)

The interaction between leptin and melatonin has been linked to disorders of the reproductive system and other conditions. The reproductive system is very sensitive to nutrients and metabolism. Leptin has a major role in the regulation of food intake and body weight and metabolic gate to the reproductive system (Wade *et al.* 1996). For example, ob/ob mice are genetically infertile. Leptin treatment restores infertility in genetically interfile ob/ob mice (Chehab *et al.* 1996). Low level of circulation leptin due to food restriction is linked to reduced secretion of gonadotropins (Cunningham *et al.* 1999, Karakaş *et al.* 2005).

Melatonin regulates fat metabolism in some mammalian species (Rasmussen *et al.* 1999, Wolden-Hansen *et al.* 2000, Baltaci & Mogulkoc 2007) and Syrian hamsters show an inverse relationship between melatonin

levels and leptin concentration (Figs 4-5) (Gündüz 2002, Balkan & Gündüz 2023).

Melatonin may be the primary regulator of leptin metabolism in raccoon dogs and Syrian hamsters, as evidenced by the fact that leptin levels are reduced and circadian changes of leptin are abolished in animals treated with melatonin (Gündüz 2002, Nieminen *et al.* 2002). The melatonin hormone may have a direct impact on the ob gene's mRNA expression. Zalatan *et al.* (2001) revealed the blocking effect of melatonin on fatty acid transport through melatonin-receptor–mediated mechanism. The hypothalamus of seasonally breeding mammals such as hamsters is programmed differently for long (summer) and short (winter) days. While the hypothalamus is sensitive to the leptin hormone on short days, it becomes resistant to it on long days (Zieba *et al.* 2007). Leptin is modulated by photoperiodical signals in seasonal breeding mammals, according to that study. The role of the pineal gland hormone melatonin in controlling leptin in sheep is demonstrated by the seasonal switch to leptin response (Zieba *et al.* 2007). Melatonin regulates the energy balance by involving three steps, namely food intake, energy storage, and energy expenditure, by sending photoperiodic signals to the central nervous system.

Kisspeptin is a neuropeptide that is primarily produced in the brain of photoperiodic animals that exhibit seasonal reproduction and is thought to have significant effects on the hypothalamic-pituitary-gonadal (HPG) axis. In addition to how kisspeptin affects fertility, current research has focused on how kisspeptin regulates energy balance and body weight (Harter *et al.* 2018). One of our most recent studies found that kisspeptin mRNA expression is low during the dark phase when leptin hormone is low, but peptide release is high (Fig. 6). Although this characteristic exists in Syrian hamster species, some rat and mouse species show a more pronounced linear relationship between kisspeptin and leptin. The discovery that leptin induces kisspeptin gene expression supports the idea that kisspeptin neurons may modify energy balance (Smith *et al.* 2006, Hill *et al.* 2008). Leptin increases the expression of the kisspeptin gene. Kisspeptin neurons do not have melatonin receptors, so it is unclear where melatonin regulates kisspeptin expression (Li *et al.* 2011).

Conclusion

The circadian clock, an internal timekeeping system, has emerged as a crucial regulator of metabolism and energy balance in peripheral tissues. Beyond its well-known influence on the endocrine system, the circadian clock coordinates metabolic processes in organs such as the liver, adipose tissue, and skeletal muscle. This intricate system ensures that metabolic functions are optimally synchronized with daily fluctuations in environmental cues, such as light-dark cycles and feeding-fasting rhythms. Disruptions to the circadian clock, such as those experienced during shift work or chronic jet lag, have been associated with metabolic disorders, including obesity, insulin resistance, and dyslipidemia. Although there have been great changes in our lifestyle with industrialization, there has been no change in our genetic structure for about ten thousand years. Today, the incompatibility between genetic structure/lifestyle has paved the way for the development of many chronic diseases. Modern lifestyle has contributed to high energy consumption, unbalanced diet and sedentary lifestyle, causing obesity to become epidemic. However, studies have shown that working at night, exposure to artificial light, and reduction in sleep time, which are one of the most important changes brought about by industrialization, also contribute to the pathogenesis of obesity. Circadian (biological) clock genes and gene products that make up our biological rhythm and are affected by the sleep/wake cycle and have a critical role in important physiological pathways for metabolism. Therefore, determining the relationship between circadian system dysfunctions and changing nutritional balance and obesity development should be considered in the treatment and prevention of obesity.

The interaction between melatonin and leptin extends beyond their direct influence on each other, as they also modulate the expression of key genes involved in energy balance regulation, such as NPY and AgRP. Melatonin has been shown to suppress the expression of NPY and AgRP in hypothalamus, two neuropeptides known for their orexigenic properties, meaning that they stimulate appetite and increase food intake. This inhibition of NPY and AgRP by melatonin suggests a role in appetite regulation and satiety. On the other hand, leptin, a hormone produced by adipose tissue, acts on hypothalamus to decrease appetite and increase energy expenditure. Leptin signaling inhibits the expression of NPY and AgRP, resulting in reduced food intake and increased energy expenditure. The complex interplay between melatonin, leptin, NPY, and AgRP genes highlights the intricate regulatory mechanisms involved in maintaining energy balance and suggests potential therapeutic targets for metabolic disorders. Further research into these interactions may provide insights into the development of interventions for conditions such as obesity and overeating disorders.

Ethics Committee Approval: Since the article does not contain any studies with human or animal subject, its approval to the ethics committee was not required.

Data Sharing Statement: All data are available within the study.

Author Contributions: Concept: B.G., Design: B.G., E.İ.B., Data analysis: B.G., E.İ.B., Writing: B.G., E.İ.B.

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References

1. Al-Hussaniy, H.A., Alburghaif, A.H. & Naji, M.A. 2021. Leptin hormone and its effectiveness in reproduction, metabolism, immunity, diabetes, hopes and ambitions. *Journal of Medicine and Life*, 14(5): 600-605. https://doi.org/10.25122/jml-2021-0153

2. Balkan, E.İ. & Gündüz, B. 2023. Adult Male Syrian Hamsters (Mesocricetus auratus) Exhibit Daily Oscillations in Their Serum Levels of Melatonin and Leptin As Well As in the Expression of the GnRH, GnIH, and Kisspeptin Genes. *Türk Tarım ve Doğa Bilimleri Dergisi*, 10(1): 68-75. https://doi.org/10.30910/turkjans.1196793

3. Baltaci, A.K. & Mogulkoc, R. 2007. Pinealectomy and melatonin administration in rats: their effects on plasma leptin levels and relationship with zinc. *Acta Biologica Hungarica*, 58: 335-343. https://doi.org/10.1556/ABiol.58.2007.4.1

4. Barger, J.L., Walford, R.L. & Weindruch, R. 2003. The retardation of aging by caloric restriction: its significance in the transgenic era. *Experimental Gerontology*, 38(11-12): 1343-1351. https://doi.org/10.1016/j.exger.2003.10.017

5. Bray, M.S. & Young, M.E. 2012. Chronobiological effects on obesity. *Current Obesity Reports*, 1: 9-15. https://doi.org/10.1007/s13679-011-0005-4

6. Cano, P., Jiménez-Ortega, V., Larrad, A., Toso, C.F.R., Cardinali, D.P. & Esquifino, A.I. 2008. Effect of a high-fat diet on 24-h pattern of circulating levels of prolactin, luteinizing hormone, testosterone, corticosterone, thyroid-stimulating hormone and glucose, and pineal melatonin content, in rats. *Endocrine*, 33: 118-125. https://doi.org/10.1007/s12020-008-9066-x

7. Challet, E., Caldelas, I., Graff, C. & Pévet, P. 2003. Synchronization of the molecular clockwork by light-and food-related cues in mammals. *Biological Chemistry*, 384(5):711-9. http://doi.org/10.1515/BC.2003.079

8. Charlot, A., Hutt, F., Sabatier, E. & Zoll, J. 2021. Beneficial effects of early time-restricted feeding on metabolic diseases: importance of aligning food habits with the circadian clock. *Nutrients*, 13(5): 1405. https://doi.org/10.3390/nu13051405

9. Chehab, F.F., Lim, M.E. & Lu, R. 1996. Correction of the sterility defect in homozygous obese female mice by treatment with the human recombinant leptin. *Nature Genetics*, 12(3): 318-320. https://doi.org/10.1038/ng0396-318

10. Chen, Y., Essner, R.A., Kosar, S., Miller, O.H., Lin, Y.C., Mesgarzadeh, S. & Knight, Z. A. 2019. Sustained NPY signaling enables AgRP neurons to drive feeding. *Elife*, 8, e46348. https://doi.org/10.7554/eLife.46348

11. Coleman, D.L. 1973. Effects of parabiosis of obese with diabetes and normal mice. *Diabetologia*, 9(4): 294-298.

12. Coleman, D.L. 2010. A historical perspective on leptin. *Nature Medicine*, 16(10): 1097-1099. https://doi.org/10.1038/nm1010-1097

13. Coupé, B., Grit, I., Darmaun, D. & Parnet, P. 2009. The timing of "catch-up growth" affects metabolism and appetite regulation in male rats born with intrauterine growth restriction. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 297(3): R813-R824. https://doi.org/10.1152/ajpregu.00201.2009

14. Cunningham, M.,J., Clifton, D.K. & Steiner, R.A. 1999. Leptin's role on the reproductive axis: perspectives and mechanisms. *Biology of Reproduction* 60(2): 216-222. https://doi.org/10.1095/biolreprod60.2.216

15. O'Brien, P., Hinder, L.M., Callaghan, B.C. & Feldman, E.L. 2017. Neurological consequences of obesity. *The Lancet Neurology*, 16(6): 465-477. https://doi.org/10.1016/S1474-4422(17)30084-4

16. Froy, O. 2007. The relationship between nutrition and circadian rhythms in mammals. *Frontiers in Neuroendocrinology*, 28(2-3): 61-71. https://doi.org/10.1016/j.yfrne.2007.03.001

17. Frühbeck, G., Jebb, S.A. & Prentice, A.M. 1998. Leptin: physiology and pathophysiology. *Clinical Physiology*, 18(5): 399-419. https://doi.org/10.1046/j.1365-2281.1998.00129.x

18. Galgani, J.E., Ryan, D.H. & Ravussin, E. 2010. Effect of capsinoids on energy metabolism in human subjects. *British Journal of Nutrition*, 103(1): 38-42. https://doi.org/10.1017/S0007114509991358

19. Gündüz, B. & Hasanoğlu, N. 2016. Molecular evaluation of obesity-related hypothalamic NPY and AgRP gene expressions in melatonin injected and pinealectomized Syrian hamsters (*Mesocricetus auratus*) housed in short and long photoperio, pp. 98. Paper presented at the 41st Federation of European Physiological Congress, June 29-July 1, Paris, France.

20. Gündüz, B. 2002. Daily rhythm in serum melatonin and leptin levels in the Syrian hamster (*Mesocricetus auratus*). *Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology*, 132(2): 393-401. https://doi.org/10.1016/S1095-6433(02)00041-7

21. Gündüz, B. & Karakaş, A. 2001. Effects of photoperiod and melatonin infusions on body weight in pinealectomized juvenile siberian hamsters (*Phodopus Sungorus*). *Turkish Journal of Biology*, 25(3): 301-321.

22. Harter, C.J., Kavanagh, G.S. & Smith, J.T. 2018. The role of kisspeptin neurons in reproduction and metabolism. *Journal of Endocrinology*, 238(3): R173-R183. https://doi.org/10.1530/JOE-18-0108

23. Hepler, C., Weidemann, B.J., Waldeck, N.J., Marcheva, B., Cedernaes, J., Thorne, A.K., Kobayashi, Y., Newman, M.V., Gao, P., Shao, M., Ramsey, K.M., Gupta, R.K. & Bass, J. 2022. Time-restricted feeding mitigates obesity through adipocyte thermogenesis. *Science*, 378(6617): 276-284.6. https://doi.org/10.1126/science.abl8007

24. Hill, J.W., Elmquist, J.K. & Elias, C.F. 2008. Hypothalamic pathways linking energy balance and reproduction. *American Journal of Physiology-Endocrinology and Metabolism*, 294(5): E827-E832. https://doi.org/10.1152/ajpendo.00670.2007

25. İnan, P. & Gündüz, B. 2024. Variation of NPY and AGRP MRNA expression in Syrian hamsters according to feeding

times. *Sigma Journal of Engineering and Natural Sciences*, 42(5): 1336-1343. https://doi.org/10.14744/sigma.2023.00072

26. Jais, A. & Brüning, J.C. 2017. Hypothalamic inflammation in obesity and metabolic disease. *The Journal of Clinical Investigation*, 127(1): 24-32. https://doi.org/10.1172/JCI88878

27. Jamshed, H., Beyl, R.A., Della Manna, D.L., Yang, E.S., Ravussin, E. & Peterson, C.M. 2019. Early time-restricted feeding improves 24-hour glucose levels and affects markers of the circadian clock, aging, and autophagy in humans. *Nutrients*, 11(6): 1234. https://doi.org/10.3390/nu11061234

28. Kalra, S.P., Dube, M.G., Pu, S., Xu, B., Horvath, T.L. & Kalra, P.S. 1999. Interacting appetite-regulating pathways in the hypothalamic regulation of body weight. *Endocrine Reviews*, 20(1): 68-100. https://doi.org/10.1210/edrv.20.1.0357

29. Karakaş, A. & Gündüz, B. 2006. Suprachiasmatic nuclei may regulate the rhythm of leptin hormone release in Syrian hamsters (Mesocricetus auratus). *Chronobiology International*, 23(1-2): 225-236. https://doi.org/10.1080/07420520500545821

30. Karakaş, A., Çamsarı, Ç., Erdinç, S. & Gündüz, B. 2005. Effects of photoperiod and food availability on growth, leptin, sexual maturation and maintenance in the Mongolian gerbils (Meriones unguiculatus). *Zoological Science*, 22(6): 665-670. https://doi.org/10.2108/zsj.22.665

31. Karakaş, A., Serin, E. & Gündüz, B. 2006. Food restriction affects locomotor activity in Mongolian gerbils (Meriones unguiculatus). *Turkish Journal of Biology*, 30(1): 23-28.

32. Kennedy, G.C. 1953. The role of depot fat in the hypothalamic control of food intake in the rat. *Proceedings of the Royal Society of London. Series B-Biological Sciences*, 140(901): 578-592. https://doi.org/10.1098/rspb.1953.0009

33. Krashes, M.J., Koda, S., Ye, C., Rogan, S.C., Adams, A.C., Cusher, D.S., Maratos-Flier, E., Roth, B. L. & Lowell, B. B. 2011. Rapid, reversible activation of AgRP neurons drives feeding behavior in mice. *The Journal of Clinical Investigation*, 121(4): 1424-1428. https://doi.org/10.1172/JC146229

34. Li, A.J., Wiater, M.F., Oostrom, M.T., Smith, B.R., Wang, Q., Dinh, T.T., Roberts, B.L., Jansen, H.T. & Ritter, S. 2012. Leptin-sensitive neurons in the arcuate nuclei contribute to endogenous feeding rhythms. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 302(11): R1313-R1326. https://doi.org/10.1152/ajpregu.00086.2012

35. Li, Q., Rao, A., Pereira, A., Clarke, I.J. & Smith, J.T. 2011. Kisspeptin cells in the ovine arcuate nucleus express prolactin receptor but not melatonin receptor. *Journal of Neuroendocrinology*, 23(10): 871-882. https://doi.org/10.1111/j.1365-2826.2011.02195.x

36. Lim, K., Zimanyi, M.A. & Black, M.J. 2006. Effect of maternal protein restriction in rats on cardiac fibrosis and capillarization in adulthood. *Pediatric Research*, 60(1): 83-87. https://doi.org/10.1203/01.pdr.0000220361.08181.c3

37. Marcheva, B., Ramsey, K.M., Peek, C.B., Affinati, A., Maury, E. & Bass, J. 2013. Circadian clocks and metabolism. *Circadian Clocks*, 127-155. https://doi.org/10.1007/978-3-642-25950-0_6

38. Martin-Gronert, M.S. & Ozanne, S.E. 2006. Maternal nutrition during pregnancy and health of the offspring. Biochemical Society Transactions, 34:779-882. https://doi.org/10.1042/BST0340779

39. McArthur, A.J., Gillette, M.U. & Prosser, R.A. 1991. Melatonin directly resets the rat suprachiasmatic circadian clock in vitro. *Brain Research*, 565(1): 158-161. https://doi.org/10.1016/0006-8993(91)91748-P

40. McMillen, I.C., Adam, C.L. & Mühlhäusler, B.S. 2005. Early origins of obesity: programming the appetite regulatory system. *The Journal of Physiology*, 565(1): 9-17. https://doi.org/10.1113/jphysiol.2004.081992

41. McMillen, I.C., MacLaughlin, S.M., Muhlhausler, B.S., Gentili, S., Duffield, J.L. & Morrison, J.L. 2008. Developmental origins of adult health and disease: the role of periconceptional and foetal nutrition. *Basic & Clinical Pharmacology & Toxicology*, 102(2): 82-89. https://doi.org/10.1111/j.1742-7843.2007.00188.x

42. Meli, R., Pacilio, M., Raso, G.M., Esposito, E., Coppola, A., Nasti, A., Di Carlo, C., Nappi C. & Di Carlo, R. 2004. Estrogen and raloxifene modulate leptin and its receptor in hypothalamus and adipose tissue from ovariectomized rats. *Endocrinology*, 145(7): 3115-3121. https://doi.org/10.1210/en.2004-0129

43. Mercer, J.G., Hoggard, N., Williams, L.M., Lawrence, C.B., Hannah, L.T. & Trayhurn, P. 1996. Localization of leptin receptor mRNA and the long form splice variant (Ob-Rb) in mouse hypothalamus and adjacent brain regions by in situ hybridization. *FEBS Letters*, 387(2-3): 113-116. https://doi.org/10.1016/0014-5793(96)00473-5

44. Mohawk, J.A., Green, C.B. & Takahashi, J.S. 2012. Central and peripheral circadian clocks in mammals. *Annual Review of Neuroscience*, 35(1): 445-462. https://doi.org/10.1146/annurev-neuro-060909-153128

45. Morgan, P.J., Ross, A.W., Mercer, J.G. & Barrett, P. 2003. Circadian and Seasonal Rhythms-Photoperiodic programming of body weight through the neuroendocrine hypothalamus. *Journal of Endocrinology*, 177(1): 27-34. https://doi.org/0022-0795/03/0177-027

46. Nelson, W. & Halberg, F. 1986. Meal-timing, circadian rhythms and life span of mice. *The Journal of Nutrition*, 116(11): 2244-2253. https://doi.org/10.1093/jn/116.11.2244

47. Nieminen, P., Mustonen, A.M., Asikainen, J. & Hyvärinen, H. 2002. Seasonal weight regulation of the raccoon dog (Nyctereutes procyonoides): interactions between melatonin, leptin, ghrelin, and growth hormone. *Journal of Biological Rhythms*, 17(2): 155-163. https://doi.org/10.1177/074873040201700206

48. Oosterman, J.E., Kalsbeek, A., La Fleur, S.E. & Belsham, D.D. 2015. Impact of nutrients on circadian rhythmicity. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 308(5): R337-R350. https://doi.org/10.1152/ajpregu.00322.2014

49. Prunet-Marcassus, B., Desbazeille, M., Bros, A., Louche, K., Delagrange, P., Renard, P., Casteilla, L. & Pénicaud, L. 2003. Melatonin reduces body weight gain in Sprague Dawley rats with diet-induced obesity. *Endocrinology*, 144(12): 5347-5352. https://doi.org/10.1210/en.2003-0693

50. Qi, Y., Lee, N.J., Ip, C.K., Enriquez, R., Tasan, R., Zhang, L. & Herzog, H. 2022. NPY derived from AGRP neurons controls feeding via Y1 and energy expenditure and food foraging behaviour via Y2 signalling. *Molecular Metabolism*, 59: 101455. https://doi.org/10.1016/j.molmet.2022.101455

51. Rasmussen, D.D., Boldt, B.M., Wilkinson, C., Yellon, S.M. & Matsumoto, A.M. 1999. Daily melatonin administration at middle age suppresses male rate visceral fat, plasma leptin, and plasma insulin to youthful levels. *Endocrinology*, 140(2): 1009-1012. https://doi.org/10.1210/endo.140.2.6674

52. Reiter, R. 1974. Circannual reproductive rhythms in mammals related to photoperiod and pineal function: a review. *Chronobiologia*, 1(4):365-395

53. Schwartz, M.W., Seeley, R.J., Campfield, L.A., Burn, P. & Baskin, D.G. 1996. Identification of targets of leptin action in rat hypothalamus. *The Journal of Clinical Investigation*, 98(5): 1101-1106. https://doi.org/10.1172/JCI118891

54. Schwartz, M.W., Woods, S.C., Porte Jr, D., Seeley, R.J. & Baskin, D.G. 2000. Central nervous system control of food intake. *Nature*, *404*(6778), 661-671. hat Ovid: Schwartz: *Nature*, Volume 404(6778): 661-671. https://doi.org/10.1038/35007534

55. Selmaoui, B., Oguine, A. & Thibault, L. 2001. Food access schedule and diet composition alter rhythmicity of serum melatonin and pineal NAT activity. *Physiology & Behavior*, 74(4-5): 449-455. https://doi.org/10.1016/S0031-9384(01)00592-3

56. Shochat, T. 2012. Impact of lifestyle and technology developments on sleep. *Nature and Science of Sleep*, 19-31. https://doi.org/10.2147/NSS.S18891

57. Smith, J.T., Clifton, D.K. & Steiner, R.A. 2006. Regulation of the neuroendocrine reproductive axis by kisspeptin-GPR54 signaling. *Reproduction*, 131(4): 623-630. https://doi.org/10.1530/rep.1.00368

58. Stetson, M.H., Elliott, J.A. & Menaker, M. 1975. Photoperiodic regulation of hamster testis: circadian sensitivity to the effects of light. *Biology of Reproduction*, 13(3): 329-339. https://doi.org/10.1095/biolreprod13.3.329

59. Tacad, D.K., Tovar, A.P., Richardson, C.E., Horn, W.F., Krishnan, G.P., Keim, N.L. & Krishnan, S. 2022. Satiety associated with calorie restriction and time-restricted feeding: peripheral hormones. *Advances in Nutrition*, 13(3):792-820. https://doi.org/10.1093/advances/nmac014

60. Varela, L., Stutz, B., Song, J.E., Kim, J.G., Liu, Z.W., Gao, X.B. & Horvath, T.L. 2021. Hunger-promoting AgRP neurons trigger an astrocyte-mediated feed-forward autoactivation loop in mice. *The Journal of Clinical Investigation*, 131(10):e144239. https://doi.org/10.1172/JCI144239

61. Wade, G.N., Schneider, J.E. & Li, H.Y. 1996. Control of fertility by metabolic cues. *American Journal of Physiology-Endocrinology and Metabolism*, 270(1): E1-E19. https://doi.org/10.1152/ajpendo.1996.270.1.E1

62. Weindruch, R. & Sohal, R.S. 1997. Caloric intake and aging. *New England Journal of Medicine*, 337(14): 986-994. https://doi.org/10.1056/NEJM199710023371407

63. Wolden-Hansen, T., Mitton, D.R., McCants, R.L., Yellon, S.M., Wilkinson, C.W., Matsumoto, A.M. & Rasmussen, D.D. 2000. Daily melatonin administration to middle-aged male rats suppresses body weight, intraabdominal adiposity, and plasma leptin and insulin independent of food intake and total body fat. *Endocrinology*, 141(2): 487-497. https://doi.org/10.1210/endo.141.2.7311

64. WHO (World Health Organization). 2021. Obesity and overweight. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. (Date accessed: 10.06.2022).

65. Zalatan, F., Krause, J.A. & Blask, D.E. 2001. Inhibition of isoproterenol-induced lipolysis in rat inguinal adipocytes in vitro by physiological melatonin via a receptor-mediated mechanism. *Endocrinology*, 142(9): 3783-3790. https://doi.org/10.1210/endo.142.9.8378

66. Zhang, Y., Proenca, R., Maffei, M., Barone, M., Leopold, L. & Friedman, J. M. 1994. Positional cloning of the mouse obese gene and its human homologue. *Nature (London)* 372: 425–432. https://doi.org/10.1038/372425a0

67. Zieba, D.A., Klocek, B., Williams, G.L., Romanowicz, K., Boliglowa, L. & Wozniak, M. 2007. In vitro evidence that leptin suppresses melatonin secretion during long days and stimulates its secretion during short days in seasonal breeding ewes. *Domestic Animal Endocrinology*, 33(3): 358-365. https://doi.org/10.1016/j.domaniend.2006.06.004