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Circadian Rhythm and Leptin Hormone Responses to Nutritional Restriction in Gerbils (*Meriones unguiculatus*) with Suprachiasmatic Nucleus Lesions

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Abstract: Rhythmically-regulated feeding behavior is in harmony with physiologic and metabolic activities in mammals. This rhythmic regulation is orchestrated by Suprachiasmatic Nucleus (SCN). However, it is not entirely clear how the SCN, which generates endogenous (internal) rhythms, influences body weight and serum leptin profile with activity rhythms in relation to feeding timing. In this study, animals in long photoperiod (14L:10D) were divided into two groups as control (sham-SCNx) and SCN lesions (SCNx). Then, these groups were split into four separate subgroups: a) ad libitum feeding; b) feeding only during the dark phase; c) feeding only during the light phase; and d) feeding during a specific period of the day (11:00-14:00 h). Locomotor activity and leptin hormone changes were observed in animals fed in cages attached to activity wheels for one month. Under the conditions of food restriction, the locomotor activities of the groups with SCNx and sham-SCNx demonstrated a phase shift toward the time of feeding. Serum leptin level did not change with feeding conditions but decreased in lesioned groups (SCNx). In conclusion, nutritional restriction caused phase shifts in activity rhythms and it was found that the SCN in gerbils was in charge of these rhythmic changes in the presence and absence of nutrients.

Keywords: Activity, body weight, biological clock, feeding.

Besin Kısıtlaması Uygulanan Suprakiazmatik Nükleus Lezyonlu Gerbillerde (*Meriones unguiculatus*) Sirkadiyen Ritim ve Leptin Hormon Yanıtları

Öz: Ritmik olarak düzenlenen beslenme davranışı, memelilerdeki fizyolojik ve metabolik aktivitelerle uyum içindedir. Bu ritmik düzenleme Suprakiyazmatik Nükleus (SCN) tarafından yönetilir. Ancak endojen (iç) ritimler üreten SCN'nin beslenme zamanlamasına bağlı olarak vücut ağırlığını ve serum leptin profilini aktivite ritimleriyle nasıl etkilediği tam olarak açık değildir. Bu çalışmada, uzun fotoperiyottaki (14L:10D) hayvanlar kontrol (sham-SCNx) ve SCN lezyonları (SCNx) olmak üzere iki gruba ayrıldı. Daha sonra bu gruplar a) Ad libitum; b) Sadece gece fazında beslenme; c) Sadece gündüz fazında beslenme ve d) Günün belirli bir zamanında (11:00-14:00) beslenme olmak üzere dört ayrı alt gruba ayrıldı. Bir ay boyunca aktivite tekerleklerine bağlı kafeslerde beslenen hayvanlarda lokomotor aktivite ve leptin hormonu değişiklikleri gözlendi. Besin kısıtlaması koşulları altında, SCNx ve sham-SCNx'li grupların lokomotor aktiviteleri, beslenme zamanına doğru bir faz kayması göstermiştir. Serum leptin düzeyi beslenme koşullarına göre değişmedi ancak lezyonlu gruplarda (SCNx) azalmıştır. Sonuç olarak, beslenme kısıtlamasının aktivite ritimlerinde faz kaymalarına neden olduğu ve gerbillerde SCN'nin besin varlığında ve yokluğunda bu ritmik değişikliklerden sorumlu olduğu belirlendi.

Anahtar kelimeler: Aktivite, vücut ağırlığı, biyolojik saat, beslenme.

1. Introduction

Circadian rhythm (from Latin *circa Diem*, about a day) in mammals is controlled by the suprachiasmatic nucleus (SCN) which is located at the anterior hypothalamus (Moore et al,. 2002). Maintaining a biological rhythm in humoral, behavioral, and metabolic processes is crucially dependent on SCN (Hastings et al., 2018). Previous studies have demonstrated that the disruption of the SCN alters the rhythm in these crucial functions (Kalsbeek et al., 2001; Zhang et al., 2004; Tso et al., 2017). Circadian rhythm works autonomously but zeitgebers induce alteration in rhythmicity (Querioz et al., 2021). Light serves as the main entraining signal for circadian rhythms in mammals. However, food can also be a synchronizer. SCN controls its 24-hour period by receiving environmental cues from the retinohypothalamic tract such as light/dark cycle signals (Mieda, 2020). Both photic and non-photic cues play a role in mediating SCN. Leptin, for instance, may alter SCN's rhythm and lead to a phase shift in the circadian clock (Gündüz and Karakaş, 2011; Mendoza et al., 2011). In addition, neuronal networks between the arcuate nucleus and SCN can regulate food intake (Querioz et al., 2021). Therefore, the circadian rhythm is regulated by the interaction of the master clock, zeitgebers, peripheral oscillators (a variety of body organs), and internal factors (hormones and neuronal projections) (Querioz et al., 2021).

Leptin hormone is produced and released by adipocyte cells. Produced in proportion to fat stores, leptin serves as an essential homeostatic feedback signal that influences the hypothalamus in the brain to control food intake and energy expenditure (LeDuc and Leibei, 2019). A crucial mechanism for the clock to maintain energy balance

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is leptin-mediated feedback loop. According to Prosser and Bergeron (2003), the leptin phase advances the SCN in vitro, implying that the SCN rhythm is sensitive to leptin hormone modulation. Previous studies have demonstrated the existence of leptin receptors in SCN (Couce et al., 1997; Guan et al., 1997). The electrical activity of SCN neurons may be altered by leptin, according to research, which implies that leptin may influence how the body uses energy and how much it consumes (Inyushkin et al., 2009). SCN may be impacted by non-photic cues like restricted feeding (De Araujo et al., 2016). Research reveals that restricted feeding (RF) affects gene expression in SCN and the master clock can be reset by the signal associated with RF during constant darkness. As a result, it was proposed that SCN receives information about metabolic changes and that RF may cause synchronicity in the gene expression of SCN (Nováková et al., 2011; Abe et al., 2007). Food restriction during the inactive phase causes food anticipatory behavior which raises animal locomotor activity.

Studies have shown that Mongolian gerbils (*Meriones unguiculatus*) are nocturnal or engage in crepuscular behavior (Klaus et al., 2000; Weinert et al., 2003; Hurtado-Parrado et al., 2019). Furthermore, Mongolian gerbils are a great model for studies on physiological changes brought on by feeding schedules due to their sensitivity to environmental changes (Karakaş et al., 2006). However, it is still unknown how SCN affects weight, the serum leptin profile, and locomotor activity in relation to feeding behavior. Because of these reasons, we looked at how different feeding strategies affected the locomotor activity and serum leptin profiles of male Mongolian gerbils with SCN lesions in an effort to determine how the SCN and nutrition in these rodents are related.

2. Material and Methods

2.1. Animals

The experiments were conducted on male adult Mongolian gerbils that were bred and raised in our laboratory at the Canakkale Onsekiz Mart University (age range: 3 – 4 months). Animals (n = 64) were maintained in plastic cages (16 × 31 × 42 cm) with pine shaving used as bedding in a light-dark (LD) cycle providing 14 h of light daily (06:00 – 20:00 h) in a temperature-controlled room (24°C) with humidity of 50 ± 10% in air-ventilated rooms before experimentation. All lighting was provided by cool-white, fluorescent tubes (> 200 lux) controlled by automated, programmable timers.

Animals were divided into two groups as SCN-lesioned (SCNx) (n = 32) and sham-SCNx (n = 32) animals. Additionally, each group was divided into 4 subgroups based on the amount of food they were allowed to consume: a) animals were fed ad libitum; b) animals were fed during the light phase (n = 8, food was given at 06:00 and taken back at 20:00); c) animals were fed during the dark phase (n = 8, food was given at 20:00 and taken back at 06:00); or d) animals were fed at a specific time of the day (n = 8, food was given at 11:00 and taken back at 14:00) (Fig. 1). For a month, the animals had access to food depending on the time of administration while continuous access to water was provided. The animals were handled and cared for in accordance with the experimental protocols approved by the Institutional Animal Care and Use Committee (permit no:2011/08-03) as well as the European Council on Animal Care guidelines. Every effort was made to minimize the number of animals used and their suffering.

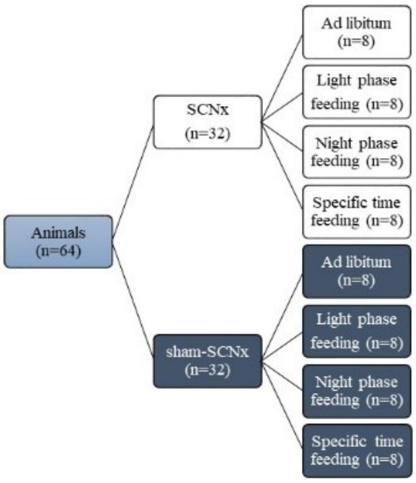


Figure 1. Design of the experiment

2.2. SCN lesions

To show entrainment, the running wheel rhythmicity of adult gerbils kept in individual housing under LD14:10 was recorded for at least a week before the experiment. The 32 rhythmic gerbils were anesthetized intraperitoneally with pentobarbital (32.5 mg/kg body weight, Sigma Chemical Company, St. Louis, Missouri, USA) and subcutaneously with ketamine (20 mg/kg body weight, Sigma Chemical Company, St. Louis, Missouri, USA) before being placed in a stereotaxic instrument. After drilling a hole in the skull, an electrode was inserted into the SCN region using stereotaxic coordinates (anterior +0.6 mm, lateral from midline +0.1 mm, and ventral -6.8 mm relative to bregma). Lesions were created by injecting current (4 mA for 10 sec) through an electrode made of stainless-steel wire that was insulated except for the tip (0.3 mm). The gerbil was placed back in the running wheel cage following the lesioning of the SCN for a week of recovery before tracking locomotor activity once more. In experiments, only animals (n = 32) with successful SCN lesion (arrhythmia) were used. At the end of the experiments, the hamsters' brains were histologically examined to confirm the lesions. A similar procedure was used in sham SCNx groups (n = 32) but no lesion was created.

2.3. Wheel running activity

Wheel running activity was recorded by a data acquisition system (Mini Mitter Company, Bend, Oregon, USA). Each of the polypropylene cages used to house the gerbils had a running wheel (10 cm in diameter) attached to a microswitch that was mounted on the outside of the cage. Vital View Software (Mini Mitter Company, Bend, Oregon, USA) was used to record the number of wheel rotations per unit time and plot them using the standard double-plotting actogram format for every 5-min bin.

2.4. Hormone measurement

Under light ether anesthesia, 0.5 - 1.0 mL blood samples from each animal's orbital sinus were taken at 12:00 h for leptin measurements. Over the course of a month, blood samples were taken once a week. The withdrawn blood was immediately replaced with an equal volume of intraperitoneally given 0.9% NaCl. Serum were frozen at -20°C after centrifuging blood samples at 4.000 rpm for 30 min at 4°C. Commercial enzyme-linked immunosorbent assay (ELISA) kits (ICN, USA) were used to measure leptin level at 450 nm. (Gündüz, 2002).

2.5. Statistics

SPSS was used to analyze the data (SPSS Inc., Statistical Software, Ver. 18.0, Chicago, Illinois, USA). One-way ANOVA was used to analyze hormone levels, followed by Duncan's multiple range test. t-tests were used to determine whether there were differences in means within or between groups. At $p < 0.05$, values were considered statistically significant. The data is presented as mean ± SEM.

3. Results

3.1. Locomotor activitiy

The locomotor activity of control animals (sham-SCNx) over the course of 30 days is shown in Figure 2. Locomotor activity is the highest in the dark phase and lowest in the light phase in animals fed ad libitum. These rhythms remained constant throughout the experiment. Although locomotor activity in animals fed only during the dark phase occurs similarly to that in animals fed ad libitum, there is less activity per unit time. In contrast, locomotor activity in animals that were only fed during the light phase occurred during the dark phase for the first five days before shifting to feeding time the following days. Even though it seemed like activity in the feeding rhythm from 11:00 to 14:00 was in a dark phase, there was actually a shift towards those hours. Figure 3 shows the locomotor activity according to feeding times in animals with SCN lesion. Locomotor activity is entirely absent in animals fed ad libitum and the animals exhibit arrhythmia. Even though SCNx animals only received dark phase feedings lost locomotor activity and exhibited arrhythmic characteristics, it was found that rhythmic activity in the dark phase began to increase on day 11 despite the animals' loss of locomotor activity. Despite having arrhythmic characteristics, SCNx animals fed only during the light phase show a shift in rhythmic activity toward the feeding phase starting on day 15. Although arrhythmic activity was observed in SCNx animals fed between 11:00 and 14:00 of the day, from the 9th day onwards, the hours with the highest locomotor activity were the hours when food was given.

3.2. Results

The leptin levels of the control (sham-SCNx) and SCNx animals on day 30 are shown in Figure 4. Comparing the SCN lesion groups to the control, leptin levels fell in each group ($p<0.05$).

4. Discussion

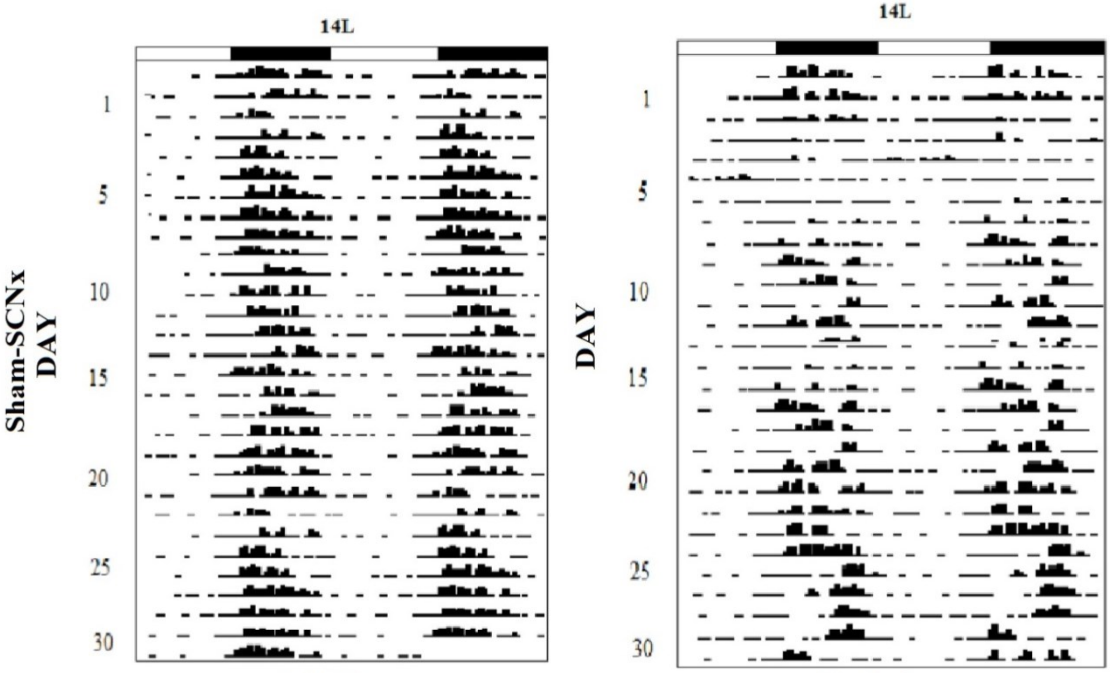
Two important time cues that affect circadian timing are daily variations in light and food availability. The circadian circuits of nutritional factors and feeding timing, however, are poorly understood. Here, we offer convincing evidence that, in addition to feeding restrictions, leptin and SCN are related. In the current study, feeding restriction in Mongolian gerbils led to phase changes in the rhythm of their locomotor activity. SCN regulates the present physiological rhythms whether food is present or not.

Numerous studies have demonstrated that the SCN, also known as the master biological clock, controls the rhythms of metabolism, hormones, and behavior. SCN lesion or ablation results in the loss of these biological rhythms (Zhang et al., 2004; Guzmán-Ruiz et al., 2014; Colwell et al., 2015). Additionally, a recent study showed that SCN (SCN^{VIP}) neurons that express vasoactive intestinal polypeptide maintained a variety of biological processes, such as body temperature, locomotor activity, the sleep-wake cycle, and gonadal hormones. Furthermore, both photic and non-photic sensory inputs may act as a mediator for these specific neurons. Disruption of these neurons consequently results in irregularities in body temperature, sleep-wake cycles, and locomotor activity (such as arrhythmia) (Todd et al., 2020).

Our results showed that food restriction caused changes in the activity phases of the animals. In response to food restrictions, a variety of species, such as Syrian hamsters, mice, rats, gerbils, rabbits, and others, display food anticipatory behavior (Holmes & Mistlgerber, 2000; Mistlberger, 2009; Karakaş, 2011; Chabot et al., 2012; Caba & Mendoza, 2018). It is unknown if the brain has a similarly distinct group of food-entrainable circadian oscillators that regulate physiological rhythms via neural and/or endocrine outputs to peripheral organs and drive behavior related to anticipating food despite the research suggesting that stimulation of food anticipatory activity follows neural and peripheral factors (Acosta-Galvan et al., 2011). Even though the circadian rhythm was lost after SCN ablation, food restriction restored the food anticipatory rhythms. The SCN controls a number of daily rhythms, including those relating to hormones, body temperature, nutrition, and locomotion as well as the auxiliary organs connected to them. Because a timing mechanism (likely neural) with circadian characteristics controls locomotor activity, eating is temporally restricted to produce food anticipatory activity. This leads to the suggestion of a food-entrainable system which may interact with the SCN and aid in the coordination of behavior and the physiological rhythm of mealtime (Mistlberger, 2011).

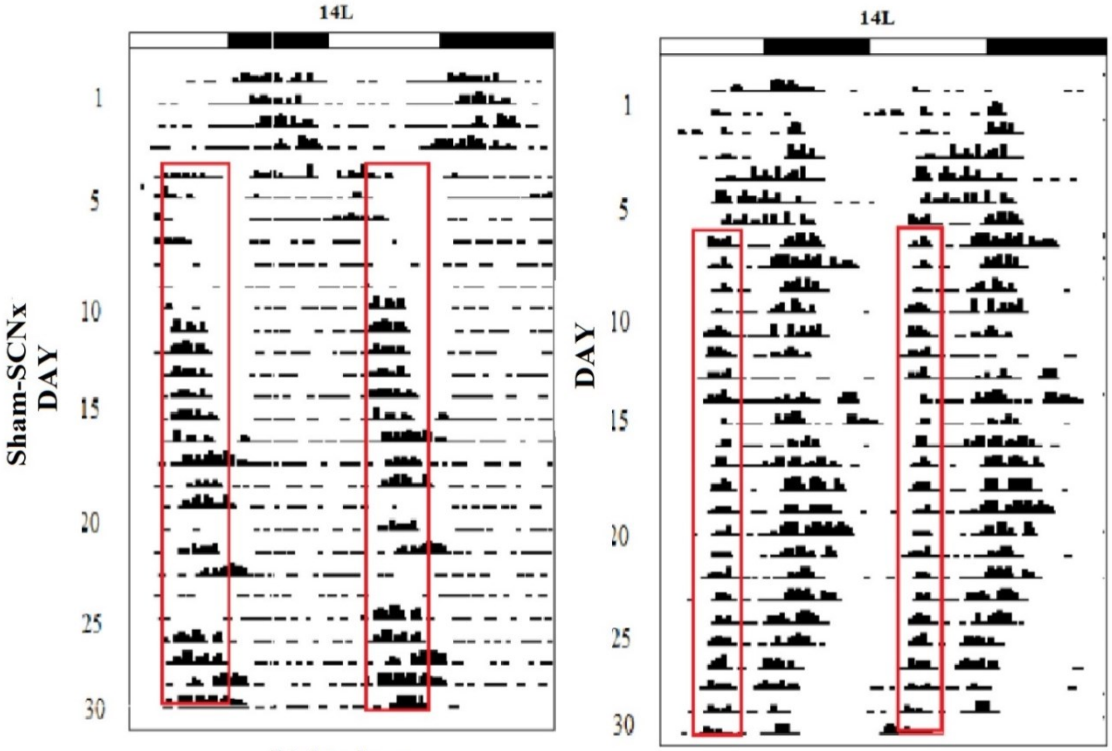
Independent of the SCN, the circadian rhythms of peripheral organs may be reprogrammed in response to dietary restrictions and other nutritional challenges. SCN-related neural pathways either stimulate or inhibit locomotor activity. However, it is also been claimed that restricted feeding only entrained peripheral organs that lacked SCN (Hara et al., 2001). It has been proposed that the SCN synchronizes other peripheral clocks using hormones or body temperature in nocturnal animals that were fed ad libitum during the light/dark cycle. SCN regulates feeding behavior in this condition. Food is the most powerful zeitgeber during the day when eating is restricted, and it affects the peripheral organs ((Damiola et al., 2000).

Food restriction and photoperiod affect the physiology and behavior of Mongolian gerbils (Karakaş, 2011). Constant light in rats eliminates the rhythms of activity when food is easily accessible. However, in conditions of restricted food intake in constant light, distinct patterns of locomotor activity appeared and this activity was synchronized to the time of feeding (Lamont et al., 2005). The phase change in locomotor activity noticed during food restriction would be brought on by the melatonin hormone. Research demonstrated that restricting food also resulted in modifications to the melatonin rhythm's phase (Challet et al.,1997). Since the melatonin receptor is expressed in the CNS, modifications to the melatonin rhythm may result in modifications to SCN activities (Liu et al.,1997). Furthermore, earlier studies showed that by implementing a food restriction, Syrian hamsters with impaired activity under constant light conditions could regain their regular activity rhythms controlled by SCN (Mistlberger, 2011). Studies have also shown that pregnant animals fed a restricted diet exhibit arrhythmia in their SCN when exposed to continuous light. Restricted feeding allowed the fetal clock and the pregnant rats' locomotor activity to both return to normal (Nováková et al., 2010). Therefore, it seems that restricting food is an effective non-photic cue that changes activity rhythms and that SCN, the master clock, regulates these physiological rhythms both in the presence and absence of food.



Ad libitum

Dark phase



Light phase

11:00-14:00

Figure 2. Changes in locomotor activity in sham-SCNx Mongolian gerbils with a different feeding schedule. The black bar in the figure represents the dark period, the white bar represents the light period, and the Y axis represents the days. The phase shift is indicated by red boxes and red lines

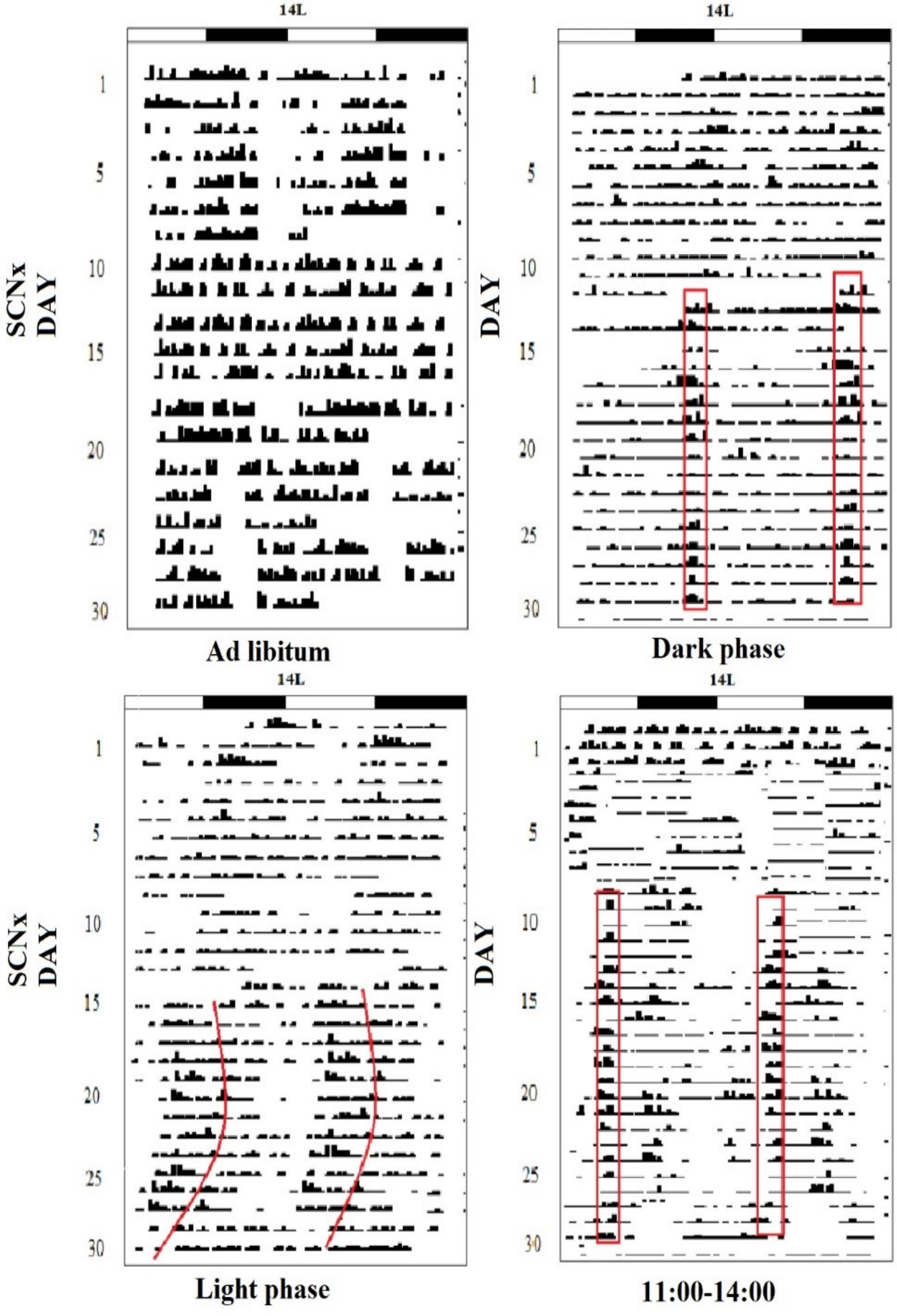


Figure 3. Changes in locomotor activity in SCNx Mongolian gerbils with a different feeding schedule. The black bar in the figure represents the dark period, the white bar represents the light period, and the Y axis represents the days. The phase shift is indicated by red boxes and red lines

Given that the SCN is a structure at the center of the circadian system, it may be crucial to understand how light- and food-entrainable components interact in order to explain the outcomes more fully. The majority of non-SCN circadian oscillators in vivo are entrained preferentially by feeding time. As a result, restricting a rat or mouse to a single meal per day during the light phase of the day when they ordinarily consume little food causes many of their organs' clock gene rhythms to realign with respect to food intake (Schibler et al., 2003; Davidson et al., 2003). The circadian clock genes in the brain undergo additional rhythmic changes and this results in an increase in locomotor activity (such as wheel running) that gradually rises before meals and peaks just before meals. In free-feeding rats and mice, SCN ablation eliminates circadian rhythmicity; however, if food intake is restricted to one meal per day, food-anticipatory rhythms reappear (Stephan et al., 1979; Marchant and Mistlberger, 1997). The SCN and peripheral clocks may lose their rhythmic relationship with one another as a result of the SCN master clock being out of phase with these food-regulated clocks which will eventually have detrimental effects on metabolic health (Mukherji et al., 2015). Studies have focused on the part of the rat brain that controls the activity related to anticipating food. Food anticipatory activity (rhythms) was found to be largely unaffected by the partial or complete removal of the neocortex, hippocampus, amygdala, nucleus accumbens, stria terminalis bed nucleus, preoptic region, and thalamic region in the brain (Mistlberger and Mumby, 1992; Davidson et al., 2000; Landry et al., 2007). Additionally, we showed that leptin was connected to the master clock SCN separately from feeding restriction. Leptin hormone is an adipokine that has a circadian rhythm in both its release from fat tissue and its central signaling (Kettner et al., 2015; Karakaş and Gündüz, 2006). The modulatory effect of NPY may allow afferent projections from arcuate nucleus to the SCN to contribute to the control of appetite (Inyushkin et al., 2018). We can therefore speculate that SCN may actually be the primary regulator of leptin (Kalsbeek et al., 2001; Karakaş and Gündüz, 2006). The results of the current study appear to be consistent with those of other studies. Given that only the SCNx group's serum leptin level decreased regardless of when they were eating, it is likely that leptin hormone is connected to SCN.

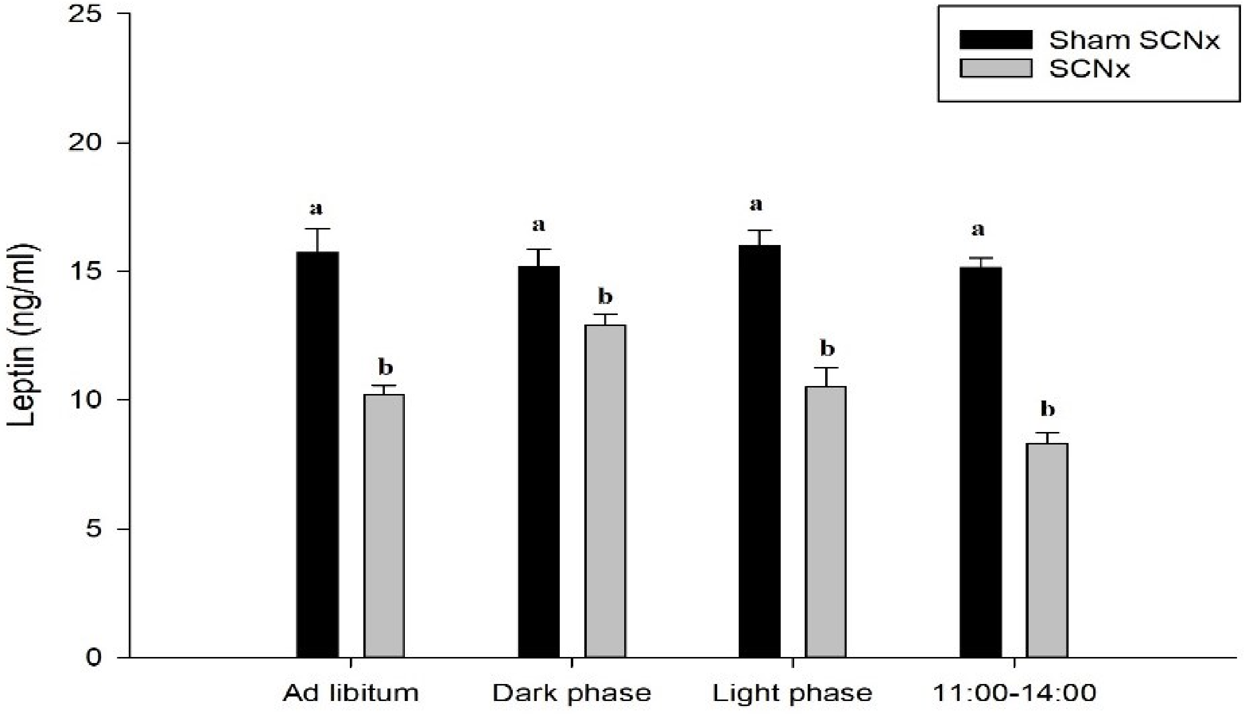


Figure 4. Weekly variations in serum leptin levels in Mongolian gerbils fed at different times. Similar letters indicate groups that are statistically similar (p>0.05)

In summary, our research suggests that a strong non-photic cue, such as food restriction, can cause Mongolian gerbils to shift their locomotor activity into a different phase. Leptin hormone can also be modulated by SCN without a feeding restriction which is another finding of the study.

Ethics committee approval: This study was performed in accordance with ethical standards of animal experiments. Legal research ethics committee approval permissions for the study were obtained from the Çanakkale Onsekiz Mart University, Animal Experiments Local Ethics Committee (No: 2011/08-03).

Conflict of interest: The authors declare that there is no conflict of interest.

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References

Abe, H., Honma, S., & Honma, K.I. (2007). Daily restricted feeding resets the circadian clock in the suprachiasmatic nucleus of CS mice. *American Journal of Physiology - Regulatory Integrative and Comparative Physiology*, 292(1), 607–615. https://doi.org/10.1152/ajpregu.00331.2006

Acosta-Galvan, G., Yi, C.X., Van Der Vliet, J., Jhamandas, J. H., Panula, P. Angeles-Castellanos, M., …………. & Buijs, R.M. (2011). Interaction between hypothalamic dorsomedial nucleus and the suprachiasmatic nucleus determines intensity of food anticipatory behaviour. *Proceedings of the National Academy of Sciences of the United States of America*, 108(14), 5813–5818. https://doi.org/10.1073/pnas.1015551108

Caba, M., & Mendoza, J. (2018). Food-anticipatory behavior in neonatal rabbits and rodents: An update on the role of clock genes. *Frontiers in Endocrinology*, 9, 266. https://doi.org/10.3389/fendo.2018.00266

Chabot, C.C., Connolly, D.M., & Waring, B.B. (2012). The effects of lighting conditions and food restriction paradigms on locomotor activity of common spiny mice, *Acomys cahirinus*. *Journal of Circadian Rhythms,* 10(6). https://doi.org/10.1186/1740-3391-10-6

Challet, E., Pévet, P., Vivien-Roels, B., & Malan, A. (1997). Phase-advanced daily rhythms of melatonin, body temperature, and locomotor activity in food-restricted rats fed during daytime. *Journal of Circadian Rhythms,* 12(1), 65–79. https://doi.org/10.1177/074873049701200108

Colwell, C.S., Witkovsky, P., & Silver, R. (2015). The suprachiasmatic nucleus (SCN): Critical points. In: Colwell CS (Ed.) Circadian Medicine. Wiley Blackwell, 37-55.

Couce, M.E., Burguera, B., Parisi, J.E., Jensen, M.D., & Lloyd, R.V. (1997). Localization of leptin receptor in the human brain. *Neuroendocrinology,* 66(3), 145–150. https://doi.org/10.1159/000127232

Damiola, F., Le Minli, N., Preitner, N., Kornmann, B., Fleury-Olela, F., & Schibler, U. (2000). Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. *Genes and Development,* 14(23), 2950–2961. https://doi.org/10.1101/gad.183500

Davidson, A.J., Cappendijk, S.L., & Stephan, F.K. (2000). Feeding-entrained circadian rhythms are attenuated by lesions of the parabrachial region in rats. *American Journal of Physiology - Regulatory Integrative and Comparative Physiology*, 278(5), R1296-R1304

Davidson, A.J., Poole, A.S., Yamazaki, S., & Menaker, M. (2003). Is the food-entrainable circadian oscillator in the digestive system? *Genes, Brain and Behavior,* 2(1), 32-39

De Araujo, L.D., Roa, S. L., Bueno, A.C., Coeli-Lacchini, F.B., Martins, C.S., Uchoa, E.T., ………… & De Castro, M. (2016). Restricted feeding schedules modulate in a different manner the expression of clock genes in rat hypothalamic nuclei. *Frontiers in Neuroscience*, 10. https://doi.org/10.3389/fnins.2016.00567

Guan, X. M., Hess, J. F., Yu, H., Hey, P. J., & Van Der Ploeg, L.H.T. (1997). Differential expression of mRNA for leptin receptor isoforms in the rat brain. *Molecular and Cellular Endocrinology,* 133(1), 1–7. https://doi.org/10.1016/S0303-7207(97)00138-X

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.

Gündüz, B., & Karakaş, A. (2011). Leptin hormonunun Suriye hamsterlerinde (*Mesocricetus auratus*) lokomotor aktivite üzerine etkileri. *Turkish Journal of Biology*, 35(6), 727–734. https://doi.org/10.3906/biy-1008-63

Guzmán-Ruiz, M., Saderi, N., Cazarez-Márquez, F., Guerrero-Vargas, N. N., Basualdo, M.C., Acosta-Galván, G., & Buijs, R.M. (2014). The suprachiasmatic nucleus changes the daily activity of the arcuate nucleus α-MSH neurons in male rats. *Endocrinology,* 155(2), 525–535. https://doi.org/10.1210/en.2013-1604

Hara, R., Wan, K., Wakamatsu, H., Aida, R., Moriya, T., Akiyama, M., & Shibata, S. (2001). Restricted feeding entrains liver clock without participation of the suprachiasmatic nucleus. *Genes to Cells,* 6(3), 269–278. https://doi.org/10.1046/j.1365-2443.2001.00419.x

Hastings, M.H., Maywood, E.S., & Brancaccio, M. (2018). Generation of circadian rhythms in the suprachiasmatic nucleus. *Nature Reviews Neuroscience,* 19(8), 453–469. https://doi.org/10.1038/s41583-018-0026-z

Holmes, M.M., & Mistlberger, R.E. (2000). Food anticipatory activity and photic entrainment in food-restricted BALB/c mice. *Physiology and Behavior,* 68(5), 655–666. https://doi.org/10.1016/S0031-9384(99)00231-0

Hurtado-Parrado, C., Cardona-Zea, Á., Arias-Higuera, M., Cifuentes, J., Muñoz, A., Rico, J. L., & Acevedo-Triana, C. (2019). Behavioral patterns of laboratory Mongolian gerbils by sex and housing condition: a case study with an emphasis on sleeping patterns. *Journal of Veterinary Behavior*, 30, 69–79. https://doi.org/10.1016/j.jveb.2018.12.004

Inyushkin, A.N., Bhumbra, G. S., & Dyball, R.E. J. (2009). Leptin modulates spike coding in the rat suprachiasmatic nucleus. *Journal of Neuroendocrinology,* 21(8), 705–714. https://doi.org/10.1111/j.1365-2826.2009.01889.x

Inyushkin, A.N., Petrova, A.A., & Tkacheva, M.A. (2018). Effects of neuropeptide Y on the functional state of the afferent inputs from the arcuate nucleus to the suprachiasmatic nucleus in rats in vitro. *Neuroscience and Behavioral Physiology,* 48(4), 511–520. https://doi.org/10.1007/s11055-018-0593-5

Kalsbeek, A., Fliers, E., Romijn, J. A., La Fleur, S. E., Wortel, J., Bakker, O., … & Buijs, R. M. (2001). The suprachiasmatic nucleus generates the diurnal changes in plasma leptin levels. *Endocrinology,* 142(6), 2677–2685. https://doi.org/10.1210/endo.142.6.8197

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

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.

Karakaş, A. (2011). The effects of photoperiod and age on food anticipatory activity in Mongolian gerbils (*Meriones unguiculatus*). *Biological Rhythm Research,* 42, no. 1, 53–65. https://doi.org/10.1080/09291011003729239

Kettner, N.M., Mayo, S.A., Hua, J., Lee, C., Moore, D.D., & Fu, L. (2015). Circadian dysfunction induces leptin resistance in mice. *Cell Metabolism,* 22(3), 448–459. https://doi.org/10.1016/j.cmet.2015.06.005

Klaus, U., Weinandy, R., & Gattermann, R. (2000). Circadian activity rhythms and sensitivity to noise in the Mongolian gerbil (*Meriones unguiculatus*). *Chronobiology International,* 17(2), 137–145. https://doi.org/10.1081/CBI-100101038

Lamont, E.W., Renteria Diaz, L., Barry-Shaw, J., Stewart, J., & Amir, S. (2005). Daily restricted feeding rescues a rhythm of period2 expression in the arrhythmic suprachiasmatic nucleus. *Neuroscience,* 132(2), 245–248. https://doi.org/10.1016/j.neuroscience.2005.01.029

Landry, G.J., Yamakawa, G.R.S., & Mistlberger, R.E. (2007). Robust food anticipatory circadian rhythms in rats with complete ablation of the thalamic paraventricular nucleus. *Brain Research,* 1141, 108-118. https://doi.org/10.1016/j.brainres.2007.01.032

LeDuc, C.A., & Leibel, R.L. (2019). Auto-Regulation of Leptin Neurobiology. *Cell Metabolism,* 30(4), 614–616. https://doi.org/10.1016/j.cmet.2019.09.006

Liu, C., Weaver, D.R., Jin, X., Shearman, L.P., Pieschl, R.L., Gribkoff, V.K. & Reppert, S.M. (1997). Molecular dissection of two distinct actions of melatonin on the suprachiasmatic circadian clock. *Neuron*, 19, 91-102. http://doi.org/10.1016/S0896-6273(00)80350-5

Marchant, E.G., & Mistlberger, R.E. (1997). Anticipation and entrainment to feeding time in intact and SCN-ablated C57BL/6j mice. *Brain Research,* 765(2), 273-282. http://doi.org/10.1016/S0006-8993(97)00571-4

Mendoza, J., Lopez Lopez, C., Revel, F.G., Jeanneau, K., Delerue, F., Prinssen, E.,.…….& Grundschober, C. (2011). Dimorphic effects of leptin on the circadian and hypocretinergic systems of mice. *Journal of Neuroendocrinology,* 23(1), 28–38. https://doi.org/10.1111/j.1365-2826.2010.02072.x

Mieda, M. (2020). The central circadian clock of the suprachiasmatic nucleus as an ensemble of multiple oscillatory neurons. *Neuroscience Research*, 156, 24–31. https://doi.org/10.1016/j.neures.2019.08.003

Mistlberger, R.E. (2009). Food-anticipatory circadian rhythms: Concepts and methods. *European Journal of Neuroscience,* 30(9), 1718–1729. https://doi.org/10.1111/j.1460-9568.2009.06965.x

Mistlberger, R.E. (2011). Neurobiology of food anticipatory circadian rhythms. *Physiology and Behavior,* 104(4), 535–545. https://doi.org/10.1016/j.physbeh.2011.04.015

Mistlberger, R.E., & Mumby, D. (1992). The limbic system and food-anticipatory circadian rhythms in the rat: ablation and dopamine blocking studies. *Behavioural Brain Research,* 47(2), 159-168. https://doi.org/10.1016/S0166-4328(05)80122-6

Moore, R.Y., Speh, J. C., & Leak, R.K. (2002). Suprachiasmatic nucleus organization. *Cell and Tissue Research,* 309(1), 89–98. https://doi.org/10.1007/s00441-002-0575-2

Mukherji, A., Kobiita, A., Damara, M., Misra, N., Meziane, H., Champy, M.F., & Chambon, P. (2015). Shifting eating to the circadian rest phase misaligns the peripheral clocks with the master SCN clock and leads to a metabolic syndrome. *Proceedings of the National Academy of Sciences,* 112(48), E6691-E6698

Nováková, M., Polidarová, L., Sládek, M., & Sumová, A. (2011). Restricted feeding regime affects clock gene expression profiles in the suprachiasmatic nucleus of rats exposed to constant light. *Neuroscience,* 197, 65–71. https://doi.org/10.1016/j.neuroscience.2011.09.028

Nováková, M., Sládek, M., & Sumová, A. (2010). Exposure of pregnant rats to restricted feeding schedule synchronizes the SCN clocks of their fetuses under constant light but not under a light-dark regime. *Journal of Biological Rhythms,* 25(5), 350–360. https://doi.org/10.1177/0748730410377967

Prosser, R.A., & Bergeron, H.E. (2003). Leptin phase-advances the rat suprachiasmatic circadian clock in vitro. *Neuroscience Letters,* 336(3), 139–142. https://doi.org/10.1016/S0304-3940(02)01234-X

Queiroz, J. do N., Macedo, R.C.O., Tinsley, G.M., & Reischak-Oliveira, A. (2021). Time-restricted eating and circadian rhythms: the biological clock is ticking. *Critical Reviews in Food Science and Nutrition*, 61(17), 2863-2875. https://doi.org/10.1080/10408398.2020.1789550

Schibler,U., Ripperger, J., & Brown, S.S. (2003). Peripheral circadian oscillators in mammals: time and food. *Journal of Biological Rhythms,* 18(3), 250-260. https://doi.org/10.1177/0748730403018003007

Stephan, F.K., Swann, J.M., & Sisk, C.L. (1979). Entrainment of circadian rhythms by feeding schedules in rats with suprachiasmatic nucleus lesions. *Behavioral and Neural Biology,* 25(4), 545-554. https://doi.org/10.1016/s0163-1047(79)90332-7.

Todd, W. D., Venner, A., Anaclet, C., Broadhurst, R. Y., De Luca, R., Bandaru, S.S., ………. & Fuller, P.M. (2020). Suprachiasmatic VIP neurons are required for normal circadian rhythmicity and comprised of molecularly distinct subpopulations. *Nature Commununacations,* 11(1), 1–20. https://doi.org/10.1038/s41467-020-17197-2

Tso, C. F., Simon, T., Greenlaw, A. C., Puri, T., Mieda, M., & Herzog, E.D. (2017). Astrocytes regulate daily rhythms in the suprachiasmatic nucleus and behaviour. *Current Biology,* 27(7),1055–1061. https://doi.org/10.1016/j.cub.2017.02.037

Weinert, D., Nevill, A., Weinandy, R., & Waterhouse, J. (2003). The development of new purification methods to assess the circadian rhythm of body temperature in Mongolian gerbils. *Chronobiology International,* 20(2), 249–270. https://doi.org/10.1081/CBI-120018649

Zhang, S., Zeitzer, J.M., Yoshida, Y., Wisor, J.P., Nishino, S., Edgar, D.M., & Mignot, E. (2004). Lesions of the suprachiasmatic nucleus eliminate the daily rhythm of hypocretin-1 release. *Sleep,* 27(4), 619–627. https://doi.org/10.1093/sleep/27.4.619