



**HAL**  
open science

## Distinct feedback actions of behavioural arousal to the master circadian clock in nocturnal and diurnal mammals

Pawan Kumar Jha, Hanan Bouâouda, Andries Kalsbeek, Etienne Challet

### ► To cite this version:

Pawan Kumar Jha, Hanan Bouâouda, Andries Kalsbeek, Etienne Challet. Distinct feedback actions of behavioural arousal to the master circadian clock in nocturnal and diurnal mammals. *Neuroscience and Biobehavioral Reviews*, 2021, 123, pp.48-60. 10.1016/j.neubiorev.2020.12.011 . hal-03366312

**HAL Id: hal-03366312**

**<https://hal.science/hal-03366312>**

Submitted on 5 Oct 2021

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Journal Pre-proof

Distinct feedback actions of behavioural arousal to the master circadian clock in nocturnal and diurnal mammals

Pawan Kumar Jha, Hanan Bouâouda, Andries Kalsbeek, Etienne Challet



PII: S0149-7634(20)30687-4  
DOI: <https://doi.org/10.1016/j.neubiorev.2020.12.011>  
Reference: NBR 4003

To appear in: *Neuroscience and Biobehavioral Reviews*

Received Date: 6 June 2020  
Revised Date: 16 September 2020  
Accepted Date: 10 December 2020

Please cite this article as: Jha PK, Bouâouda H, Kalsbeek A, Challet E, Distinct feedback actions of behavioural arousal to the master circadian clock in nocturnal and diurnal mammals, *Neuroscience and Biobehavioral Reviews* (2021), doi: <https://doi.org/10.1016/j.neubiorev.2020.12.011>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier.

## **Distinct feedback actions of behavioural arousal to the master circadian clock in nocturnal and diurnal mammals**

Pawan Kumar Jha<sup>1,2,3#\*</sup>, Hanan Bouâouda<sup>1#</sup>, Andries Kalsbeek<sup>2,3</sup> and Etienne Challet<sup>1</sup>

<sup>1</sup>Circadian Clocks and Metabolism team, Institute of Cellular and Integrative Neurosciences, Centre National de la Recherche Scientifique (CNRS), University of Strasbourg, France

<sup>2</sup>Department of Endocrinology and Metabolism, Amsterdam University Medical Center (AUMC), University of Amsterdam, The Netherlands

<sup>3</sup>Hypothalamic Integration Mechanisms, Netherlands Institute for Neuroscience, Amsterdam, The Netherlands

\*Corresponding author: Pawan K Jha; Email: kj.pawan@gmail.com

Present address: Department of Systems Pharmacology & Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA.

#These authors contributed equally.

### **Highlights**

- Behavioural arousal affects circadian rhythms in mammals by its feedback action on the master clock in the suprachiasmatic nucleus (SCN).
- In nocturnal animals arousing stimuli in the middle of the rest period induce a phase advance and attenuate light-induced phase-shifts.
- Unlike photic signals, the feedback of behavioural arousal to the SCN utilizes a network of connections involving several brain nuclei and neurotransmitters.
- Circadian responses to behavioural feedback in diurnal species differ from those in nocturnal species, indicating distinct circadian windows of sensitivity to arousal.
- It is imperative to understand this disparity in more detail before addressing the question of therapeutic interventions to repair circadian misalignments due to disturbed sleep, shift work, or trans-meridian travel.

### **Abstract**

The master clock in the suprachiasmatic nucleus (SCN) of the hypothalamus provides a temporal pattern of sleep and wake that - like many other behavioural and physiological rhythms - is oppositely phased in nocturnal and diurnal animals. The SCN primarily uses environmental light, perceived through the retina, to synchronize its endogenous circadian rhythms with the exact 24h light/dark cycle of the outside world. The light responsiveness of the SCN is maximal during the night in both nocturnal and diurnal species. Behavioural arousal during the resting period not only perturbs sleep homeostasis, but also acts as a potent non-photic synchronizing cue. The feedback action of arousal on the SCN is mediated by processes

involving several brain nuclei and neurotransmitters, which ultimately change the molecular function of SCN pacemaker cells. Arousing stimuli during the sleeping period differentially affect the circadian system of nocturnal and diurnal species, as evidenced by the different circadian windows of sensitivity to behavioural arousal. In addition, arousing stimuli reduce and increase light resetting in nocturnal and diurnal species, respectively. It is important to address further the question of circadian impairments associated with shift work and trans-meridian travel not only in the standard nocturnal laboratory animals, but also in diurnal animal models.

**Keywords:** Behavioural arousal, Circadian rhythm, Diurnal, Entrainment, Nocturnal, Phase-shifts, Sleep, Suprachiasmatic nucleus

### ***Introduction***

The 24-h period of Earth's rotation is correlated with oscillations in many critical variables in the environment, such as ambient illumination and temperature, but also the availability of nutrients and activity of predators. The periodicity of these challenges and opportunities permits an anticipation to them that will shape the temporal organization of behaviour and physiology of organisms. Different patterns of rest/activity or sleep/wake cycles segregate organisms into nocturnal, diurnal and crepuscular species. To perform optimally in their respective temporal niche, these organisms display daily oscillations in behaviour, physiology and endocrine function. Such rhythms are generated by endogenous circadian clocks expressed in most cells and tissues that oscillate with a period close to 24 h even in absence of external variations in the environment. The adaptive benefit of having such circadian clocks has been noted in various experimental setups (Sharma, 2003; Bloch et al., 2013).

In mammals, the circadian system consists of input pathways, a master pacemaker located in the hypothalamic suprachiasmatic nuclei (SCN), extra-SCN oscillators/clocks throughout the brain and body, and output pathways to enforce daily changes in the temporal organization of behaviour and physiology (Kalsbeek et al., 2006; Golombek and Rosenstein, 2010). The SCN is a heterogeneous structure that contains a varied population of neuronal and glial cell types. A recent single-cell RNA sequencing study describes five distinct neuronal and seven other major cell types in the mouse SCN (Wen et al., 2020). Anatomically, it can broadly be divided into two sub-regions based on the expression of different neuropeptides. The 'core' in its ventrolateral part is characterized by the vasoactive intestinal polypeptide (VIP) expressing neurons that receive heavy inputs from the retina and other brain areas, whereas the neurons in

the dorso-medial 'shell' predominantly express arginine vasopressin (AVP) and receive fewer extra-SCN innervations (Abrahamson and Moore, 2001; Morin, 2007). The circadian rhythms generated in the SCN are driven by the expression of core clock genes and their intertwining interactions, as well as by the strong intercellular coupling between the SCN cells (Ko and Takahashi, 2006; Liu et al., 2007). Among mammalian species, most daily endocrine, behavioural and physiological rhythms are differently phased depending upon their temporal niche (Challet, 2007; Jha et al., 2015). These differences are schematically illustrated in **Fig. 1A-D**. However, the daily pattern of SCN activity is relatively similar across species. In particular, the molecular clockwork in the SCN is similarly phased according to astronomical time. For instance, the daily peak of expression of the clock gene *Per1* in the SCN occurs around noon in both nocturnal and diurnal mammals (Sun et al., 1997; Takumi et al., 1998; Mrosovsky et al., 2001; Caldelas et al., 2003; Otalora et al., 2013). In the same line, the electrical activity of the SCN is higher during daytime compared to the night in nocturnal as well as diurnal animals (Smale et al., 2003). Furthermore, rhythmic outputs from the SCN studied so far are similarly phased according to astronomical time in the two categories of animals (e.g., peak of release of SCN vasopressin always in late daytime). By contrast, brain structures targeted by the SCN efferents, such as the paraventricular nucleus of the hypothalamus, interpret the temporal messages coming from the SCN differently in diurnal and nocturnal species (Kalsbeek et al., 2008).

For optimal adaptability, the circadian rhythms of an organism must be synchronized with the predictable changes in the environment. Various stimuli, broadly classified into either photic or non-photoc cues, have the ability to reset and entrain the circadian system. It is well established that forced wakefulness or induced arousal acts as a non-photoc clue that feeds back to the SCN clock in nocturnal animals (Turek, 1989; Mrosovsky, 1996; Hughes and Piggins, 2012; Webb et al., 2014). Considering that the temporal organization of the sleep and wakefulness cycle is oppositely phased in nocturnal and diurnal species, the feedback action of arousal may not be the same in diurnal and nocturnal species. Indeed, comparative studies suggest that behavioural arousal affects the master clock and its light resetting differently in nocturnal and diurnal mammals. The aim of this review is to discuss how induced arousal, or involuntary wakefulness, feeds back to the SCN clock and exerts its phase resetting and entraining action in nocturnal and diurnal animals.

### ***Light entrainment of the SCN clock***

Light is the most ubiquitous entraining *Zeitgeber* (time giver) encountered in the daily life of most organisms. Photic entrainment may influence, and be influenced by, the non-photic phase resetting in mammals. Therefore, we must first discuss photic entrainment in brief here. As by definition the period of endogenous circadian rhythms differs slightly from 24-h in most mammals, therefore rhythms must periodically be shifted either forward or backward in order to maintain an appropriate phase-relationship with the environmental period of exactly 24-h (Challet, 2007). Brief pulses of light delivered to animals housed in constant darkness produce phase-dependent shifts in the timing of their rest-activity cycles, thereby defining a so-called phase-response curve (PRC) to light (Daan and Pittendrigh, 1976; Schwartz and Zimmerman, 1990). Exposure to light during the late day and early night, when nocturnal animals have just become active after dusk and diurnal animals start their resting period, delays the SCN clock. Consequently, this shift will also delay the SCN-controlled rest/activity rhythm to a slightly later time on subsequent cycles, re-adjusting the rhythm phase with the external world, especially for animals with an endogenous period shorter than 24 h. On the other hand, light exposure during the late night and early morning (i.e., close to activity offsets and onsets in nocturnal and diurnal species, respectively) advances the phase of the SCN clock. As a result, this shift will advance the rest/activity rhythm to a slightly earlier time on subsequent days, re-adjusting the behaviour and physiology with the external environment, especially for animals with an endogenous period longer than 24 h. Furthermore, during most of the day, light has no phase-shifting effect. These circadian responses to light are roughly similar in both nocturnal and diurnal species (**Fig. 2A-D**) (Caldelas et al., 2003; Slotten et al., 2005; Challet, 2007).

Phase-shifts such as those described above in response to light pulses are generally evaluated by measurements of daily onsets or offsets of the locomotor activity pattern. As mentioned above, these shifts in rhythmic behaviour correspond to phase-changes of the underlying SCN clock. How does light reset the SCN clock? In 1972 Moore and Lenn discovered terminals of retinal axons in the SCN, strongly suggesting that the mammalian retina could convey photic information to the SCN (Moore and Lenn, 1972). It is now well established that photic signals from the retina are conveyed to the SCN mainly via a direct pathway called the retinohypothalamic tract (RHT), in addition to rods and cones involving photosensitive retinal ganglion cells (Moore and Lenn, 1972; Rea, 1998; Hattar et al., 2002) (**Fig. 3**). The axons of these retinal ganglion cells project mono-synaptically to the core (ventral) of the SCN (Hattar et al., 2002), where they release mainly glutamate and PACAP (Castel et al., 1993; Hannibal et al., 1997). Additionally, an indirect neural pathway courses to the SCN via the

intergeniculate leaflet (IGL) (Moore and Card, 1994; Hattar et al., 2006). From the IGL, the geniculohypothalamic tract (GHT) projects to the SCN and thus indirectly conveys light information (Pickard et al., 1987). The delay between RHT and GHT signals may provide additional information leading to a more differentiated response of the SCN to light cues. Other structures could also transmit light information to the SCN indirectly. For example, the lateral hypothalamic area (LH) is also a target of the RHT (Hattar et al., 2006) and the arousal-promoting orexin neurons in the LH project to the immediate vicinity of the SCN (McGranaghan and Piggins, 2001; Brown et al., 2008). The downstream signaling of the photic pathways induces acute expression of several immediate early genes, such as *c-fos*, and the clock genes *Per1* and *Per2* (Kornhauser et al., 1990; Albrecht et al., 1997; Shigeyoshi et al., 1997).

Moreover, the effect of light is not only limited to these transcriptional changes, but it also impacts on post-transcriptional modifications of core clock components. For example, light-induced degradation of the clock protein BMAL1 may constitute an important step for photic entrainment (Tamaru et al., 2000). The intricacy of photic entrainment is getting even more intensified by epigenetic modifications, such as light-induced chromatin remodeling within SCN cells (Crosio et al., 2000).

### ***Reciprocal interactions between homeostatic sleep response and SCN clock***

The circadian timing of wake and sleep is one of the characteristics that distinguish diurnal and nocturnal animals. It is noteworthy that the sleep-wake cycle is an extensively studied behavioural rhythm in mammals. In addition to its circadian modulation, homeostatic regulation of sleep is another important physiological process that separately and interactively controls its quality, timing and duration (Franken, 2013; Borbely et al., 2016). The homeostatic process of sleep is regulated by the interactive action of arousal and sleep promoting areas in mammalian brain, primarily located in the hypothalamus and brainstem (Saper and Fuller, 2017). Regarding the circadian modulation of sleep, the SCN is involved in the regulation of the circadian architecture of sleep propensity, sleep onset and its maintenance (Dijk et al., 1997; Lavie, 1997; Sack et al., 1997; Dijk and Duffy, 1999).

The pathways that mainly stimulate wake maintenance consist of glutamatergic inputs from parabrachial and pedunculopontine tegmental nuclei to the basal forebrain, and GABAergic and cholinergic neurons in the basal forebrain that innervate the cerebral cortex. In addition, GABAergic neurons in LH promote wakefulness by inhibiting sleep-promoting neurons in the

thalamus and preoptic area (Herrera et al., 2016; Venner et al., 2016). On the other hand, circuitries that contribute to promotion of sleep lie mainly in the hypothalamic ventrolateral preoptic (VLPO) and median preoptic (MnPO) areas. Sleep-active GABAergic neurons of preoptic areas project to the above-mentioned wake-active components and inhibit them in a regulated fashion. Furthermore, brainstem GABAergic neurons inhibit glutamatergic arousal neurons and promote sleep (Saper and Fuller, 2017). As such, the wake-sleep regulatory circuit seems to act as self-regulatory loop in which activity in one limb stops input from the other one and vice-versa. How the central pacemaker in the SCN controls the circadian timing of wake and sleep is not fully clear yet. There are possibilities that the SCN communicates to wake and sleep areas in the brain through direct and indirect connections. A sparse input from the SCN to the VLPO implicates a direct influence of the pacemaker on this sleep centre (Chou et al., 2002). The SCN also sends major outputs to the subparaventricular zone and to the dorsomedial hypothalamic nucleus (DMH). In turn, the DMH sends GABAergic projections to the VLPO and glutamatergic projections to the LH (Chou et al., 2003).

The evidence that emerges from both animal and human studies shows that the homeostatic sleep response (process S) and the circadian process (process C) both act independently, but also interact continuously (Borbely et al., 2016). Efficient sleep homeostasis in SCN-ablated rats and bright light-induced phase-shifts in human subjects are indicative of independent functioning of both processes (Tobler et al., 1983; Dijk and Beersma, 1989; Trachsel et al., 1992). The SCN clock may interact with sleep homeostasis by influencing the rise and fall of sleep pressure in a time-of-the day dependent manner. The circadian phase during which prolonged waking occurs, modifies the level of subsequent sleep propensity (Werth et al., 1996; Vyazovskiy et al., 2007). At the molecular level, the role of clock genes in sleep homeostasis has been documented (Deboer, 2007; Franken, 2013). Mice knock-out for clock genes (*Per1-3*, *Clock*, *Bmal1*, Cryptochrome: *Cry1* and *Cry2*, *Npas2*), show not only disabled circadian clocks, but also an abnormal sleep phenotype and modified sleep homeostasis (Franken, 2013). This indicates that circadian clocks influence sleep homeostasis also at the molecular level. Most likely, clock genes expressed in extra-SCN brain regions are involved in the homeostatic mechanism of sleep. Results of *in situ* hybridization experiments revealed that *Per2* expression in cortex, forebrain and thalamic nuclei increases in response to sleep loss and returns to control levels within 2-h of sleep recovery (Franken et al., 2007; Franken, 2013). Remarkably, sleep deprivation does not affect expression of *Per2* in the SCN (Curie et al., 2015). How sleep-wake states influence clock genes and other rhythmically expressed genes is not clearly understood



yet. New experiments aiming to study gene expression in the SCN and elsewhere in the brain during sleep deprivation and recovery sleep over a few circadian cycles would help to better understand how the sleep homeostasis interacts with the circadian pacemaker in the SCN. Accordingly, a recent study indicates that sleep deprivation abolishes protein oscillations in the mice forebrain (Noya et al., 2019).

Now the question arises: does the functioning of the SCN clock change according to sleep homeostasis? Much research has been done in this direction during the last few decades (Turek, 1989; Mrosovsky, 1996; Hughes and Piggins, 2012; Webb et al., 2014). These studies are based on involuntarily arousal that not only changes the sleep architecture, but also changes the photic response and phase shifting capacity of the SCN pacemaker. As it will be summarised in the following sections, these responses are often very different in nocturnal and diurnal animals.

### ***Arousal: A potent non-photic cue***

The concept of non-photic entrainment of circadian rhythms came forward through a series of experiments demonstrating that the rhythms of birds could be entrained to the daily playback of bird's songs (Gwinner, 1966a, b; Menaker and Eskin, 1966). The early reports of social entrainment in humans (Aschoff, 1979; Wever, 1979) also strengthened the notion of light-independent entrainment of circadian rhythms. Further, it was reported that enhanced locomotion had the ability to act as a potent *Zeitgeber* in nocturnal rodents and humans (Yamada et al., 1986; Reebbs and Mrosovsky, 1989a; Buxton et al., 1997). In addition to that, meal timing also emerged as a strong synchronizing signal of peripheral circadian clocks in mammals, while scheduled feeding modified the temporal niche of behavioural activity in both nocturnal and diurnal species (Challet, 2010; Vivanco et al., 2010b; Patton and Mistlberger, 2013). Another possible non-photic synchronizer is external temperature, which is very efficient to entrain circadian clocks in heterothermic animals as well as in plants (Rensing and Ruoff, 2002). In most endothermic mammals, episodes of hypothermia can phase-shift secondary clocks with no major effect on the main SCN clock (Buhr et al., 2010). Of note, entrainment of the master clock by cycles of high ambient temperature has been identified in the diurnal *Octodon degus*, camel and goat (Vivanco et al., 2010a; El Allali et al., 2013; Farsi et al., 2020).

The first evidence of behavioural arousal as a synchronizing factor came from experiments with dark pulses in the nocturnal insectivorous bat, *Taphozous melanopogon*, housed in constant dim light (Subbaraj and Chandrashekar, 1978). Exposure to dark pulses in the

resting phase resulted in phase-advances, while dark pulses in their active phase resulted in phase-delays. As in bats, dark pulses in nocturnal rodents housed in constant light produced large advances in the mid-to-late subjective day and smaller phase-delays in late subjective night (Challet, 2007; Webb et al., 2014). In the dark pulse experiments, clock resetting occurs mostly during the resting period, irrespective of the opposite circadian pattern of locomotor activity between nocturnal and diurnal species (Lee and Labyak, 1997; Mendoza et al., 2007). Since darkness induces hyperactivity and/or arousal in nocturnal animals, it has been proposed that hyperactivity in these species mediates part of the resetting properties of dark exposure (Reebs et al., 1989; Canal and Piggins, 2006). Other procedures that stimulate arousal during the usual daily resting period, such as induced locomotor activity, introduction of a (novel) running wheel or sleep deprivation, produce phase-shifts comparable to those induced by dark pulses (Reebs and Mrosovsky, 1989b; Antle and Mistlberger, 2000).

On the other hand, our study in the diurnal grass rat, *Arvicanthis ansorgei* suggests that sleep deprivation in the early rest (night) period induces phase-delays, thus mimicking photic resetting, not dark-induced resetting (Jha et al., 2017). These findings indicate that circadian sensitivity to non-photic cues may differ greatly between nocturnal and diurnal animals (**Fig 4A-B**). Moreover, the cues associated with behavioural activation, such as involuntary physical activity, sleep deprivation, adenosinergic or serotonergic activation, all decrease photic responses of the SCN clock in nocturnal rodents (Watanabe et al., 1996; Mistlberger et al., 1997; Challet et al., 2001; Elliott et al., 2001; Sigworth and Rea, 2003), whereas the same treatments increase photic responses in the diurnal grass rat (Cuesta et al., 2008; Jha et al., 2017). On the other hand, in both diurnal and nocturnal rodents, some other procedures leading to arousal, such as caffeine and modafinil treatment, proved to be ineffective to induce behavioural phase-shifts (Webb et al., 2006; Vivanco et al., 2013; Jha et al., 2017).

#### *Arousal can be linked to physical exercise*

A number of methods, which include confinement to a novel wheel, injection of benzodiazepine that triggers locomotor activity, and forced treadmill running, were used to study the enhanced levels of locomotor activity and their effects on circadian functions (Turek and Losee-Olson, 1986; Mrosovsky and Salmon, 1987; Mistlberger, 1991). It has been shown that single discrete, locomotor activity pulses induced during the mid-to-late part of the subjective day lead to phase-advances of free-running activity rhythms in nocturnal hamsters (Reebs et al., 1989; Reebs and Mrosovsky, 1989b). Triazolam, a short-acting benzodiazepine, and confinement to a novel running wheel also produce this shifting effect in hamsters housed

in constant conditions (Turek and Losee-Olson, 1986; Turek and Losee-Olson, 1987). The PRCs to both triazolam (Turek and Losee-Olson, 1986) and novel wheel-induced locomotor activity pulses (Reebs and Mrosovsky, 1989b), similarly define a typical non-photoc profile, with maximal phase-advances of 2-3 h, when activity is induced during the mid-to-late subjective day and somewhat smaller phase-delays during the late subjective night (Reebs and Mrosovsky, 1989b; Wickland and Turek, 1991; Smith et al., 1992). The magnitude of phase-shifts resulting from induced locomotor activity is dose-dependent (i.e., correlated with the amount of locomotor activity performed) (Wickland and Turek, 1991; Janik and Mrosovsky, 1993; Weisgerber et al., 1997; Bobrzynska and Mrosovsky, 1998). Running during three consecutive hours is necessary to induce maximal responses in hamsters (Reebs and Mrosovsky, 1989a; Wickland and Turek, 1991). The same procedure also leads to sizeable phase-shifts in nocturnal mice housed in constant darkness (Challet et al., 2000). Therefore, the circadian system of nocturnal rodents has a relatively high threshold for exercise to alter circadian function, at least compared to light, which produces measurable phase-shifts after as little as a few minutes of exposure to low-intensity light (Takahashi et al., 1984; Sharma and Chandrashekar, 1997). The relatively low sensitivity to locomotor activity feedback may represent a buffering system to prevent inappropriate phase-shifting to weak arousal or small amounts of motor activity outside the main active period.

The effects of enhanced locomotor activity on the circadian system have not been studied extensively yet in diurnal rodents. Previous studies in the diurnal European ground squirrel and Common marmoset investigated the phase-shifting effect of induced locomotor activity (Hut et al., 1999; Glass et al., 2001). Because of the small phase-advances observed during the late subjective day, the authors concluded that the responses of the SCN clock to the non-photoc stimuli were close to those in nocturnal rodents. This conclusion, however, was based mostly on analysis of the phase-angle of entrainment, not PRC, to single stimuli. Also results from studies with human subjects indicate significant effects of exercise on the circadian system. Daily exercise facilitates phase-delays of melatonin secretion (Barger et al., 2004). Van Cauter and colleagues showed that physical activity in early and mid-night induces respective phase-advances and delays (Van Reeth et al., 1994; Buxton et al., 1997), highlighting clear phase-dependent effects. The study of exercise PRC in humans demonstrated afternoon phase-advances and early night phase-delays (Youngstedt et al., 2019), consistent with our study of sleep deprivation in the diurnal grass rat. Interestingly, chronotype of person influences the circadian rhythm phase shifts cause by timed exercise (Thomas et al., 2020).

*Arousal can be independent of physical exercise*

In the studies that implicate high-intensity locomotor activity (forced or voluntary exercise) as the main phase-shifting stimulus, sleep loss or non-specific arousal may participate in the phase-shifting process as well, independently of locomotion *per se*. Animals that run little after an arousing stimulus may fail to shift because they do not stay awake, whereas animals that do display a phase-shift after intense running may do so because they remain awake. The possibility of a potential contribution of non-specific arousal to non-photic stimuli was already mentioned in early experiments on non-photic resetting (Mrosovsky, 1988; Rusak et al., 1989). Furthermore, brief arousing episodes induced by an intraperitoneal injection of saline were even able to produce phase-shifts without substantial locomotor activity, though the magnitude of shifts remained much smaller (Hastings et al., 1998). Antle and Mistlberger (2000) showed in Syrian hamsters that the phase-shifting effects of intense locomotor activity can be fully mimicked by keeping animals awake by gentle handling, with minimal levels of motor activity (Antle and Mistlberger, 2000). Because sleep deprivation leads to accumulation of extracellular adenosine in the central nervous system, experiments aimed at mimicking sleep deprivation used intracranial or intraperitoneal injection of an adenosine A1 agonist. When administered during the mid-sleep period, these adenosinergic compounds produce dose-dependent shifts similar to those induced by sleep deprivation in nocturnal hamsters. Accordingly, the adenosine antagonist caffeine fails to induce phase-shifts in these animals, but it attenuates the shifts induced by sleep deprivation (Antle et al., 2001). Like caffeine, other psychostimulant drugs, such as methamphetamine and modafinil, also show chronobiotic inefficacy in nocturnal rodents (Vivanco et al., 2013).

The behavioural responses to arousing cues that are relatively independent of locomotor activity are largely unknown in the diurnal rodents. Our study in the diurnal grass rat, *Arvicanthis ansorgei*, suggests that sleep deprivation (provoked by gentle handling) in the early night induces phase-delays, while this awaking procedure in late resting (night) period remained ineffective to shift the SCN clock. Results from human studies indicate that one night of sleep deprivation, during which subjects were asked not to perform physical activity, led to phase-delays of plasma melatonin rhythm (Cajochen et al., 2003). Consistent with previous reports in nocturnal animals, caffeine treatment alone does not induce any behavioural phase-shift in diurnal rodents either (Jha et al., 2017). In addition, it is noteworthy that cohabitation, which could have some arousing components, influences the circadian rhythms in diurnal

rodents, such as *Octodon degus* and *Arvicanthis niloticus* (Goel and Lee, 1997; Castillo-Ruiz et al., 2018).

#### *Interactions between arousal and photic entraining stimuli*

In laboratory conditions, the environmental variables are tightly controlled in order to determine the responses to specific stimuli. By contrast, in nature it will be more common that different *Zeitgebers* act in combination. The responses of the mammalian circadian system to both photic and non-photoc stimuli are mediated by effects on the central pacemaker. Therefore, it is important to consider the convergent, yet distinct, responses of animals to a combination of non-photoc and photic signals. In this section, we describe some findings on the reciprocal interactions of behavioural arousal and photic stimuli on the master clock.

As discussed above, acute arousal due to enhanced physical exercise or sleep deprivation in the middle of rest period induces large phase-advances in nocturnal rodents housed in constant darkness. When the animal is stably entrained to an LD cycle the same stimulus has little or no detectable effect at these daily/circadian phases (daytime), i.e., when the animal is not transferred to constant darkness immediately after the stimulus (Janik et al., 1994). However, in young hamsters that are naïve to wheel running and placed in a wheel for the first time during the light portion of the LD cycle, an extended bout of running may occur. This procedure has been found, in some cases, to markedly phase-advance the rest-activity cycle, which then takes several days to be re-entrained to the LD cycle. Interestingly, if the wheel transfer is performed at the usual time of lights off, no shift is observed (Gannon and Rea, 1995).

The question arises why an arousal process during the middle of the light period normally induces little or no shift of the rest-activity rhythm in nocturnal animals housed in an LD cycle? Do arousal and light exposure work antagonistically on the circadian phase? In accordance with this hypothesis, phase-advance shifts induced by light pulses are attenuated if they are concurrent with or followed by arousing stimuli (Ralph and Mrosovsky, 1992; Mistlberger and Antle, 1998). Furthermore, sleep deprivation or injection of an adenosine A1 agonist in the middle or late light period also inhibit light-induced phase-shifts of locomotor activity rhythms in mice and hamsters (Watanabe et al., 1996; Mistlberger et al., 1997; Challet et al., 2001; Elliott et al., 2001; Sigworth and Rea, 2003). In addition, wake-promoting drugs like caffeine, methamphetamine and modafinil, slow down the photic resetting in nocturnal rodents (Moriya et al., 1996; Ono et al., 1996; Vivanco et al., 2013). Among all these wake-promoting molecules, caffeine shows inconsistency in its interaction with photic responses. Contrary to

the attenuation of photic resetting shown by a high dose of caffeine (40 mg/kg) (Vivanco et al., 2013), a moderate dose of caffeine (15 mg/kg) potentiated photic resetting in mice (van Diepen et al., 2014; Ruby et al., 2018). These findings indicate a dose-dependent, biphasic response of light-induced resetting of the nocturnal SCN clock to caffeine.

These inhibitory interactions in nocturnal rodents have been conceptualized as the result of opposite actions of photic and non-photoc stimuli on the expression of clock genes in the SCN pacemaker. Accordingly, light and behavioural arousal would respectively activate and repress transcription of the clock genes *Per1* and *Per2*. Arousal thus reverses the cellular and molecular changes that would normally shift the circadian timing loops after exposure to light (Maywood et al., 1999; Maywood and Mrosovsky, 2001). However, such a model may not be suitable to explain the shifting effects of arousal during the night in diurnal animals, that is, when the mRNA levels of *Per1* and *Per2* in the SCN are endogenously low (i.e., precluding a further “non-photoc like” down-regulation of their transcription) (Challet, 2007). On the other hand, period gene expression is about to start at this time and arousal might thus keep it from initiating its expression. Such a delayed start of its expression should also cause a phase-delay.

In addition to its acute phase-shifting effect, long-term scheduled arousal may also modulate the photic entrainment process. A remarkable example has been obtained by transferring Syrian hamsters from their home cage into a novel wheel for 3 h each day in the middle of the light period, while maintaining the LD cycle (Sinclair and Mistlberger, 1997). This repetition over one week induces a characteristic delay in the onset of nocturnal running that may exceed 6 h. This procedure seemed to split the daily activity cycle into two components when discontinuing the arousal schedule in darkness for few days (Mrosovsky and Janik, 1993; Gorman and Lee, 2001). The neural and molecular events associated with such splits are not clearly understood yet.

In contrast to the findings in nocturnal rodents, results from our experiments in the diurnal grass rat, *Arvicanthis ansorgei*, indicate that behavioural arousal independent of locomotor activity (i.e., sleep deprivation by gentle handling and caffeine-induced arousal), potentiates the phase-delays and advances induced by light exposure in early and late night, respectively (Jha et al., 2017). Some studies in humans also reported interactions between arousal and light entrainment. With respect to the chronobiotic effects of sleep deprivation in humans, partial sleep loss combined with bright light reduces light-induced phase-advances (Burgess, 2010), in contrast to the effects in diurnal grass rats in the late night (Jha et al., 2017). To our

knowledge, the combination of partial sleep deprivation and light in the early night has not been performed in humans yet, thus precluding a precise comparison with the early night data in diurnal grass rats. Also, the effects of caffeine consumption on the human circadian system have been documented. A study in blind patients indicates that daily administration of caffeine (150 mg) is not sufficient to entrain the master clock (St Hilaire and Lockley, 2015). However, caffeine consumption alone can suppress melatonin release and attenuate the nighttime decrease in body temperature in sleep-deprived subjects (Wright et al., 1997). Furthermore, evening intake of caffeine (3 mg/kg) can produce significant phase-delays of the human SCN clock, while it does not modify significantly the shifting effect of bright light (Burke et al., 2015). Considering our results in the diurnal grass rat, it could be interesting to test whether caffeine consumption in humans may not potentiate the shifting effects of light exposure with lower intensities.

### ***Brain nuclei and pathways involved in arousal-induced resetting of circadian rhythms***

The SCN afferents involved in the non-photoc modulation of circadian rhythms have been divided into two major pathways: 1) the GHT originating in the IGL, which contains NPY and GABA amongst others (Harrington et al., 1985; Moore and Card, 1994), and 2) an ascending serotonergic pathway originating in the median raphe nucleus (Meyer-Bernstein and Morin, 1996) (**Fig. 3**). Emerging evidence also relates other neurochemical (e.g. cholinergic and orexinergic) pathways to the non-photoc regulatory mechanisms of circadian phase (Webb et al., 2008; Yamakawa et al., 2016).

### ***Projections from the intergeniculate leaflet via the GHT***

The GHT is a thin elongated fiber tract arising from the IGL that projects to the ventral SCN (Morin, 2013), the IGL itself is situated between the dorsal and ventral lateral geniculate nuclei (Hickey and Spear, 1976; Pickard, 1985; Morin et al., 1992). Both acute wheel-running activity and sleep deprivation by gentle handling markedly increase c-FOS expression in IGL neurons (Janik et al., 1995; Antle and Mistlberger, 2000). Electrical stimulation of the IGL produces phase-shifts, as behavioural arousal does (Rusak et al., 1989). At the same time, ablation of this region blocks the phase-shifts to various arousing stimuli in hamsters and mice (Johnson et al., 1988; Janik and Mrosovsky, 1994; Wickland and Turek, 1994; Koletar et al., 2011). These findings suggest that activation of the IGL is necessary for circadian clock resetting mediated by arousal stimuli. In addition to NPY and GABA, the GHT may also contain enkephalin and neurotensin as neuromodulators (Morin and Blanchard, 2001). Interestingly,

lesions of the IGL also influenced the circadian behaviour of diurnal Nile grass rat, as well as their responses to light and dark pulses (Gall et al., 2013).

**Neuropeptide Y:** In hamsters, almost 50% of IGL neurons that project to the SCN are immunoreactive for NPY (Morin and Blanchard, 2001). Wheel confinement in the middle of the rest period markedly increases c-FOS expression in the IGL NPY neurons and increases the release of this peptide in the SCN (Janik et al., 1995; Glass et al., 2010). Remarkably nocturnal light pulses also induce c-FOS expression in the IGL, but not in NPY neurons (Janik et al., 1995). Intra-SCN administration of NPY results in a PRC similar to that produced by non-photoc behavioural manipulations in hamsters and mice (Biello et al., 1994; Huhman and Albers, 1994; Maywood et al., 2002; Soscia and Harrington, 2005). Blocking the effect of NPY by injection of NPY antiserum severely attenuates wheel-running-induced phase-advances without reducing the number of wheel revolutions (Biello et al., 1994). *In vitro* treatment with NPY during the subjective day dose-dependently phase-advances the peak firing rate of the SCN neurons (Medanic and Gillette, 1993; Shibata and Moore, 1993; Biello et al., 1997; Harrington and Schak, 2000). Furthermore, both *in vitro* and *in vivo* application of NPY suppresses *Per1* and *Per2* expression in the SCN (Fukuhara et al., 2001; Maywood et al., 2002). NPY may also be involved in non-photoc inhibition of photic responses, because NPY infusion into the SCN completely blocks light-induced phase-advances (Weber and Rea, 1997). In diurnal animals the role of NPY in the arousal-induced resetting of the master clock is largely unknown. However, different patterns of fluctuation of NPY in the SCN and NPY-containing neurons in IGL between nocturnal and diurnal rodents suggest a distinct role in the circadian system of both classes of animals (Smale et al., 2001; Vidal and Lugo, 2006).

**GABA:** Most of the neurons in the IGL (including those projecting to the SCN via the GHT) and SCN are GABAergic (Moore and Speh, 1993; Moore and Card, 1994; Morin and Blanchard, 2001). GABA<sub>A</sub> receptor agonists have been shown to perturb the circadian phase in hamsters and mice. Midday central administration of the GABA<sub>A</sub> agonist muscimol induces phase-advances of the behavioural rhythm (Ebihara et al., 1988; Smith et al., 1989). Intra-SCN administration of muscimol *in vivo* (Mintz et al., 2002; Ehlen and Paul, 2009) or application of muscimol *in vitro* induces non-photoc like phase-shifts in rest-activity and SCN electrical activity rhythms (Tominaga et al., 1994; McElroy et al., 2009). SCN GABA<sub>A</sub> receptor activation downstream of IGL input is also necessary for NPY-mediated clock resetting since phase-shifts to NPY are blocked by administration of the GABA<sub>A</sub> receptor antagonist



bicuculline both *in vitro* and *in vivo* (Janik et al., 1994; Huhman et al., 1997; Gribkoff et al., 1998). In the diurnal unstriped Nile grass rats, *Arvicanthis niloticus*, SCN GABAergic activation during the mid-subjective day leads to phase-delays (Smith et al., 1989; Novak and Albers, 2004). Such behavioural shifts induced by GABA<sub>A</sub> activation during the mid-subjective day have been associated with a down-regulation of *Per1* and *Per2* in the SCN of nocturnal rodents and only of *Per2* in the SCN of diurnal *Arvicanthis* (Ehlen et al., 2006; Novak et al., 2006). Moreover, GABAergic stimulation inhibits light-induced phase-shifts in both nocturnal and diurnal rodents (Gillespie et al., 1997; Novak and Albers, 2004).

**Enkephalin:** Enkephalin-containing neurons in the IGL have been reported in several species and these neurons also contribute to the GHT (Card and Moore, 1989; Smale et al., 1991; Moore and Speh, 1993; Morin and Blanchard, 1995; Morin and Blanchard, 2001). *In vivo* systemic administration of fentanyl, a relatively selective  $\mu$  receptor agonist, induces large phase-advances in hamsters when administered during the mid- to late light period. Like fentanyl treatment, similar phase-advances have been reported after morphine treatment (Chen et al., 1993; Marchant and Mistlberger, 1995; Meijer et al., 2000; Vansteensel et al., 2003; Vansteensel et al., 2005). Enkephalinergic cells have also been found in the dorsomedial SCN (Abrahamson and Moore, 2001; Morin and Allen, 2006), suggesting that release of this neuropeptide from SCN neurons may also contribute to the control of circadian phase.

**Neurotensin:** The hamster IGL also contains neurotensin-positive cells that project to the SCN (Morin and Blanchard, 2001). Neurotensin-expressing cells also have been described in the mouse ventral SCN (Abrahamson and Moore, 2001), as well as in the human SCN (Goncharuk et al., 2001). *In vitro* midday application of this neuropeptide to the rat SCN induces large phase-advances in neuronal firing rhythm (Meyer-Spasche et al., 2002).

#### *Serotonergic projections from the raphe nuclei*

Serotonin (5-HT) has long been reported to modulate circadian responses. 5-HT transmission has been proposed as a potential mediator of behavioural phase-shifts and modulation of photic synchronization by arousal (Moriya et al., 1996; Sumova et al., 1996; Watanabe et al., 1996; Morin, 1999; Grossman et al., 2000; Challet et al., 2001). The release of 5-HT associated with arousal and arousal-induced behavioural shifts most often has an inhibitory effect on photic resetting or entrainment in nocturnal rodents (Moriya et al., 1996; Sumova et al., 1996; Mistlberger and Antle, 1998; Grossman et al., 2000; Cuesta et al., 2009). In the rat, phase-shifts induced by arousal are attenuated by pre-treatment with a serotonin antagonist (Sumova et al.,

1996). In hamsters, however, phase-shifts induced by stimulated running are not blocked by 5-HT receptor antagonists or serotonin depletion in SCN (Bobrzynska et al., 1996; Antle et al., 1998), but triazolam-induced phase-shifts are blocked by removal of the SCN 5HT input, despite the lack of c-fos expression in the raphe nuclei (Cutrera et al., 1993, 1994). On the other hand, stimulated locomotor activity and sleep deprivation lead to release of serotonin in the SCN of nocturnal rodents (Dudley et al., 1998; Grossman et al., 2000).

The serotonergic projection from the median raphe innervates the SCN, while the IGL receives a serotonergic projection from the dorsal raphe (Hughes and Piggins, 2012). Waking is associated with increased firing rate of serotonergic neurons in the raphe nuclei and increased 5-HT release in the SCN and IGL (Dudley et al., 1998; Jacobs and Fornal, 1999; Barassin et al., 2002; Grossman et al., 2004). Electrical stimulation of the raphe nuclei leads to behavioural phase-shifts with increased levels of serotonin and suppressed c-FOS expression in the SCN of nocturnal species (Meyer-Bernstein and Morin, 1996; Dudley et al., 1999). Serotonin release in the SCN associated with arousal-induced phase-shifts is blocked by intra-dorsal raphe injections of 5-HT<sub>1,2,7</sub> and 5-HT<sub>7</sub> antagonists, indicating the role of dorsal raphe output in the phase-resetting response to arousal (Glass et al., 2003). It has been reported that arousal attenuates photic resetting of the SCN clock via associated serotonergic changes (Moriya et al., 1996; Ono et al., 1996; Challet et al., 2001). Furthermore, in general administration of 5-HT and 5-HT<sub>1A/7</sub> agonists to SCN slices *in vitro*, as well as in animals *in vivo* produces typical non-photoc-like PRCs, with large phase-advances during the day and small, if any, phase-delays in late night (Prosser et al., 1990; Medanic and Gillette, 1992; Tominaga et al., 1992; Edgar et al., 1993; Shibata and Moore, 1993; Bobrzynska et al., 1996; Challet et al., 1998; Ehlen et al., 2001; Horikawa and Shibata, 2004). SCN serotonin levels follow the daily pattern of activity/rest in nocturnal and diurnal rodents, with higher values during the active period (Poncet et al., 1993; Cuesta et al., 2008; Cuesta et al., 2009). Injections of serotonin, both *in vitro* and *in vivo*, are capable of phase-advancing the SCN clock during the mid-subjective day in nocturnal rodents (Shibata et al., 1992; Bobrzynska et al., 1996).

In sharp contrast, in the diurnal rat *Arvicanthis*, serotonergic receptor activation produces phase-advances essentially during the subjective night, but not during the mid-subjective day (Cuesta et al., 2008). In nocturnal rodents, the phase-shifts induced by serotonergic activation are consistently associated with reduced expression of *Per1* and *Per2* in the SCN. However, in the diurnal *Arvicanthis*, *Per* expression is unchanged after such treatment, suggesting distinct

molecular mechanisms in diurnal species that remain to be identified (Horikawa et al., 2000; Glass et al., 2001; Cuesta et al., 2008). In our recent experiments in *Arvicanthis ansorgei* where sleep deprivation and caffeine treatment enhanced photic resetting of SCN clock, we reported no change of 5-HT levels in the SCN and midbrain, whereas caffeine treatment increased midbrain serotonin (Jha et al., 2017). Furthermore, serotonin modulates photic resetting differently between nocturnal and diurnal rodents. Serotonergic activation reduces light-induced shifts in nocturnal rodents, while this treatment potentiates light-induced phase-shifts in the diurnal *Arvicanthis* (Challet et al., 2001; Cuesta et al., 2008). Consistently, a serotonergic activation induced by a single dose of citalopram, a serotonin reuptake inhibitor, increases photic sensitivity of the circadian system in humans (McGlashan et al., 2018). These results indicate that arousal feedback mediated by serotonin acts differently in nocturnal and diurnal animals.

#### *Orexinergic projections from the lateral hypothalamic area*

As already mentioned earlier, orexin-expressing neurons in the LH are important for the appropriate control of arousal (Sakurai, 2007), and innervate a number of structures implicated in arousal-mediated circadian resetting, such as IGL, median raphe and the peri-SCN region (Hughes and Piggins, 2012) (**Fig. 3**). In turn, orexinergic neurons receive indirect afferent projections from the SCN (Abrahamson and Moore, 2001; Deurveilher and Semba, 2005), suggesting reciprocal modulation between circadian and arousal-promoting circuits. It has been reported that novel wheel-running, sleep deprivation by gentle handling and dark pulses elevate c-FOS expression in orexin-expressing cells (Marston et al., 2008; Webb et al., 2008). Moreover, orexin acutely alters both SCN and IGL neuronal activity *in vitro* (Farkas et al., 2002; Brown et al., 2008; Klisch et al., 2009; Pekala et al., 2011). Of note, activation of orexinergic neurons in the LH precedes the onset of the main activity bout (Marston et al., 2008). So far, it is not fully clear whether activation of LH neurons is a consequence of non-photic-like phase-shifts or part of the upstream mechanisms controlling them.

#### *Acetylcholinergic pathways*

Two populations of cholinergic neurons project to the SCN, one from the midbrain tegmentum and another one from the basal forebrain (Bina et al., 1993). Since cholinergic neurons are involved in the regulation of sleep and arousal, these projections may well transmit behavioural cues to the SCN. Acetylcholine and cholinergic agonists applied *in vivo* or *in vitro* led to phase-advances of the SCN clock, especially at night (Trachsel et al., 1995; Liu and Gillette, 1996).

In rats, damage of cholinergic projections to the SCN reduces and increases light-induced phase-advances and delays, respectively, thus indicating that cholinergic cues modulate photic resetting (Erhardt et al., 2004). In addition, a more recent study in Syrian hamsters suggests that cholinergic cells in the basal forebrain are necessary for arousal-induced phase-shifting (Yamakawa et al., 2016).

### ***Molecular bases of arousal-induced resetting of circadian rhythms***

Arousing stimuli modify expression of immediate early genes in the circadian system. In particular, these non-photoc manipulations decrease rhythmic c-FOS expression in the SCN, while they induce its expression in the IGL of nocturnal rodents (Janik and Mrosovsky, 1992; Mistlberger et al., 1998; Antle and Mistlberger, 2000; Coogan and Piggins, 2005). In response to behavioural arousal, c-FOS expression is triggered specifically in NPYergic cells of the IGL (Janik et al., 1995), whereas a light pulse activates non-NPYergic cells in the IGL. Thus, although the IGL is involved in both non-photoc and photic entrainment, it does so through separate cell populations.

As already mentioned, the levels of *Per1* and *Per2* mRNA are rapidly down-regulated following daytime wheel-confinement in nocturnal hamsters (Maywood et al., 1999; Maywood and Mrosovsky, 2001). Similarly, *Per1* levels in the SCN decrease after sleep deprivation (Webb et al., 2014). Other non-photoc stimuli such as systemic injections of 5-HT<sub>1A/7</sub> agonist, intra-SCN NPY and dark pulses, also decrease *Per1* and *Per2* expression in the SCN (Horikawa et al., 2000; Fukuhara et al., 2001; Mendoza et al., 2004). In diurnal rodents the levels of *Per1* and *Per2* mRNA are reduced in response to dark pulses, but their expression remains unchanged after serotonergic activation (Mendoza et al., 2007; Cuesta et al., 2008), indicating distinct molecular mechanisms from those reported above in nocturnal rodents.

Serotonergic resetting of the SCN clock in nocturnal rodents is mainly mediated by 5-HT<sub>7</sub> and 5-HT<sub>1A</sub> receptors (Lovenberg et al., 1993; Cuesta et al., 2009). Activation of 5-HT<sub>7</sub> receptors leads to an increase in cyclic adenosine monophosphate (cAMP) production (Lovenberg et al., 1993). *In vitro* the circadian rhythm in electrical firing rate of the rat SCN can be shifted in a non-photoc manner by activation of the cAMP cascade (Prosser and Gillette, 1989). Protein kinase A (PKA) is activated by cAMP. In *in vitro* SCN preparations phase-shifts induced by 5-HT<sub>1A</sub> agonist can be inhibited by pretreatment of the slice with a PKA inhibitor (Prosser et al., 1994). The non-photoc-like phase-shift induced by NPY is mediated by the NPY Y<sub>2</sub> receptor (Golombek et al., 1996). Activation of this receptor leads to activation of phospholipase C and

production of inositol triphosphate and diacyl-glycerol, which then leads to release of intracellular  $\text{Ca}^{2+}$  and activation of protein kinase C (PKC). Pretreatment of SCN slices with PKC inhibitors blocks the NPY-induced phase-shifts of the circadian rhythm of electrical firing rate (Biello et al., 1997).

The MAPK family has also been implicated in non-photic and dark pulse-induced phase-shifting. Dark pulses during the subjective day and sleep deprivation suppress ERK phosphorylation in the hamster SCN (Coogan and Piggins, 2005). ERK activation may regulate transcription factors, which could lead to changes in clock gene expression. The activated form of ERK is decreased by sleep deprivation in most of the SCN cells. On the other hand, sleep deprivation activates ERK in a small dorsolateral cluster of cells in the caudal SCN (Antle et al., 2008).

### ***SCN electrical activity and clock resetting***

Electrical activity of the SCN is correlated with the rest/activity cycle in both diurnal and nocturnal mammals, i.e. with a positive correlation in diurnal animals and a negative correlation in nocturnal species (Inouye and Kawamura, 1979; Meijer et al., 1997; Meijer et al., 1998; Deboer et al., 2003). Behavioural arousal that leads to phase-shifts of the master circadian clock of nocturnal animals is associated with an acute inhibition of SCN neuronal activity, as assessed by suppression of c-FOS expression (Antle and Mistlberger, 2000). Also, in freely-moving nocturnal rats and hamsters, increased locomotor activity bouts are linked with a transient reduction of SCN firing rate, which recovers when the activity bout ceases (Meijer et al., 1997; Yamazaki et al., 1998; Schaap and Meijer, 2001). This suppression of SCN firing rate is not induced when animals perform less vigorous activities, such as grooming and feeding. The magnitude of the suppression is thus correlated with the intensity of wheel running (Yamazaki et al., 1998; Schaap and Meijer, 2001; van Oosterhout et al., 2012). Moreover, NPY, GABA and serotonin predominantly suppress SCN firing rate (Webb et al., 2014). It would be interesting to study whether behavioural arousal that phase-shifts the circadian clock in nocturnal species independently of locomotor activity, also suppresses SCN firing rate.

Furthermore, the ability of these stimuli to suppress neural activity may be crucial for resetting the molecular clock mechanism in nocturnal mice. Indeed, NPY-induced phase-advances of SCN *Per2* expression *in vitro* are blocked by  $\text{K}^+$  mediated depolarization even 2 h after NPY washout (Besing et al., 2012). Thus, long-term inhibition of SCN neural firing may be necessary to induce non-photic circadian resetting in nocturnal mammals. Because the firing

rate of the SCN is higher during the active phase in diurnal mammals, the feedback effects of behavioural arousal are expected to be quite different from those described above in nocturnal animals. Such a hypothesis deserves to be investigated in future studies.

### ***Conclusion and future directions***

Ambient light is the dominant synchronizer of the master clock in the SCN of mammals. SCN responsiveness to light is very similar in terms of circadian phase and direction of induced phase-shifts in nocturnal and diurnal species. In addition to light, behavioural arousal is another potent clock resetting stimulus. Behavioural arousal in the middle of the rest period induces characteristic phase-advances in nocturnal rodents, with arousing stimuli with or without a locomotor activity component showing a similar feedback to the SCN clock. Since the sleep/wake cycle is oppositely phased between nocturnal and diurnal species, it is important to determine the circadian sensitivity of arousal over a 24 h cycle also in diurnal species. It appears that unlike photic entrainment, arousal leads to different responses as compared to nocturnal mammals, both in humans and diurnal rodents. Moreover, interactions of arousing stimuli with photic entrainment involve different pathways or mechanisms because behavioural arousal antagonizes or potentiates the effects of light on the SCN respectively in nocturnal and diurnal mammals. Thus, various studies strengthen the notion that behavioural arousal modulates the master clock differently in nocturnal and diurnal animals to maintain their respective temporal niche. Most likely these disparities are a manifestation of their different temporal activity/rest period, species difference or cumulative effect of both. Most of the studies on mammalian circadian entrainment so far have been done with standard laboratory nocturnal rodents. Further inclusion of diurnal rodents and more studies in human subjects would help to conclude with more certainty whether circadian entrainment follows distinct patterns between these two categories of species. Furthermore, determining how arousal-promoting areas in the brain interact with the SCN and whether this wiring is different between nocturnal and diurnal animals should be studied in more detail in future experiments. Therefore, at the circuit level, new research of wake promoting areas connected to the SCN needs to be performed. In addition, further investigations of how wake-promoting molecules, like caffeine and modafinil, modulate circadian rhythms in a time-of-day dependent manner in diurnal animal models could also be helpful to develop chronotherapies and other biomedical applications to counteract or prevent circadian misalignment commonly induced by disturbed sleep, shift work, or trans-meridian travels.

### **Conflict of Interest**

The authors have no conflict of interest to declare. This review is based partly on the PhD thesis introduction of Pawan Kumar Jha entitled “Sleep deprivation and its impact on circadian rhythms and glucose metabolism” from the University of Strasbourg, Strasbourg, France and the University of Amsterdam, Amsterdam, the Netherlands.

## References

- Abrahamson EE, Moore RY (2001) Suprachiasmatic nucleus in the mouse: retinal innervation, intrinsic organization and efferent projections. *Brain Res* 916:172-191.
- Albrecht U, Sun ZS, Eichele G, Lee CC (1997) A differential response of two putative mammalian circadian regulators, *mper1* and *mper2*, to light. *Cell* 91:1055-1064.
- Antle MC, Mistlberger RE (2000) Circadian clock resetting by sleep deprivation without exercise in the Syrian hamster. *J Neurosci* 20:9326-9332.
- Antle MC, Steen NM, Mistlberger RE (2001) Adenosine and caffeine modulate circadian rhythms in the Syrian hamster. *Neuroreport* 12:2901-2905.
- Antle MC, Marchant EG, Niel L, Mistlberger RE (1998) Serotonin antagonists do not attenuate activity-induced phase shifts of circadian rhythms in the Syrian hamster. *Brain Res* 813:139-149.
- Antle MC, Tse F, Koke SJ, Sterniczuk R, Hagel K (2008) Non-photoc phase shifting of the circadian clock: role of the extracellular signal-responsive kinases I/II/mitogen-activated protein kinase pathway. *Eur J Neurosci* 28:2511-2518.
- Aschoff J (1979) Circadian rhythms: influences of internal and external factors on the period measured in constant conditions. *Z Tierpsychol* 49:225-249.
- Barassin S, Raison S, Saboureau M, Bienvenu C, Maitre M, Malan A, Pevet P (2002) Circadian tryptophan hydroxylase levels and serotonin release in the suprachiasmatic nucleus of the rat. *Eur J Neurosci* 15:833-840.
- Barger LK, Wright KP, Jr., Hughes RJ, Czeisler CA (2004) Daily exercise facilitates phase delays of circadian melatonin rhythm in very dim light. *Am J Physiol Regul Integr Comp Physiol* 286:R1077-1084.
- Besing RC, Hablitz LM, Paul JR, Johnson RL, Prosser RA, Gamble KL (2012) Neuropeptide Y-induced phase shifts of PER2::LUC rhythms are mediated by long-term suppression of neuronal excitability in a phase-specific manner. *Chronobiol Int* 29:91-102.
- Biello SM, Janik D, Mrosovsky N (1994) Neuropeptide Y and behaviorally induced phase shifts. *Neuroscience* 62:273-279.
- Biello SM, Golombek DA, Schak KM, Harrington ME (1997) Circadian phase shifts to neuropeptide Y *In vitro*: cellular communication and signal transduction. *J Neurosci* 17:8468-8475.
- Bina KG, Rusak B, Semba K (1993) Localization of cholinergic neurons in the forebrain and brainstem that project to the suprachiasmatic nucleus of the hypothalamus in rat. *J Comp Neurol* 335:295-307.
- Bloch G, Barnes BM, Gerkema MP, Helm B (2013) Animal activity around the clock with no overt circadian rhythms: patterns, mechanisms and adaptive value. *Proc Biol Sci* 280:20130019.
- Bobrzynska KJ, Mrosovsky N (1998) Phase shifting by novelty-induced running: activity dose-response curves at different circadian times. *J comp Physiol A* 182:251-258.
- Bobrzynska KJ, Godfrey MH, Mrosovsky N (1996) Serotonergic stimulation and nonphotic phase-shifting in hamsters. *Physiol Behav* 59:221-230.
- Borbely AA, Daan S, Wirz-Justice A, Deboer T (2016) The two-process model of sleep regulation: a reappraisal. *J Sleep Res* 25:131-143.
- Brown TM, Coogan AN, Cutler DJ, Hughes AT, Piggins HD (2008) Electrophysiological actions of orexins on rat suprachiasmatic neurons *in vitro*. *Neurosci Lett* 448:273-278.
- Buhr ED, Yoo SH, Takahashi JS (2010) Temperature as a universal resetting cue for mammalian circadian oscillators. *Science* 330:379-385.

- Burgess HJ (2010) Partial sleep deprivation reduces phase advances to light in humans. *J Biol Rhythms* 25:460-468.
- Burke TM, Markwald RR, McHill AW, Chinoy ED, Snider JA, Bessman SC, Jung CM, O'Neill JS, Wright KP, Jr. (2015) Effects of caffeine on the human circadian clock in vivo and in vitro. *Sci Transl Med* 7:305ra146.
- Buxton OM, Frank SA, L'Hermite-Baleriaux M, Leproult R, Turek FW, Van Cauter E (1997) Roles of intensity and duration of nocturnal exercise in causing phase delays of human circadian rhythms. *Am J Physiol* 273:E536-542.
- Cajochen C, Jewett ME, Dijk DJ (2003) Human circadian melatonin rhythm phase delay during a fixed sleep-wake schedule interspersed with nights of sleep deprivation. *J Pineal Res* 35:149-157.
- Caldelas I, Poirel VJ, Sicard B, Pevet P, Challet E (2003) Circadian profile and photic regulation of clock genes in the suprachiasmatic nucleus of a diurnal mammal *Arvicanthis ansorgei*. *Neuroscience* 116:583-591.
- Canal MM, Piggins HD (2006) Resetting of the hamster circadian system by dark pulses. *Am J Physiol Regul Integr Comp Physiol* 290:R785-792.
- Card JP, Moore RY (1989) Organization of lateral geniculate-hypothalamic connections in the rat. *J Comp Neurol* 284:135-147.
- Castel M, Belenky M, Cohen S, Ottersen OP, Storm-Mathisen J (1993) Glutamate-like immunoreactivity in retinal terminals of the mouse suprachiasmatic nucleus. *Eur J Neurosci* 5:368-381.
- Castillo-Ruiz A, Indic P, Schwartz WJ (2018) Time management in a co-housed social rodent species (*Arvicanthis niloticus*). *Sci Rep* 8:1202.
- Challet E (2007) Minireview: Entrainment of the suprachiasmatic clockwork in diurnal and nocturnal mammals. *Endocrinology* 148:5648-5655.
- Challet E (2010) Interactions between light, mealtime and calorie restriction to control daily timing in mammals. *J Comp Physiol B* 180:631-644.
- Challet E, Takahashi JS, Turek FW (2000) Nonphotic phase-shifting in clock mutant mice. *Brain Res* 859:398-403.
- Challet E, Scarbrough K, Penev PD, Turek FW (1998) Roles of suprachiasmatic nuclei and intergeniculate leaflets in mediating the phase-shifting effects of a serotonergic agonist and their photic modulation during subjective day. *J Biol Rhythms* 13:410-421.
- Challet E, Turek FW, Laute M, Van Reeth O (2001) Sleep deprivation decreases phase-shift responses of circadian rhythms to light in the mouse: role of serotonergic and metabolic signals. *Brain Res* 909:81-91.
- Chen JC, Smith ER, Cahill M, Cohen R, Fishman JB (1993) The opioid receptor binding of dezocine, morphine, fentanyl, butorphanol and nalbuphine. *Life Sci* 52:389-396.
- Chou TC, Bjorkum AA, Gaus SE, Lu J, Scammell TE, Saper CB (2002) Afferents to the ventrolateral preoptic nucleus. *J Neurosci* 22:977-990.
- Chou TC, Scammell TE, Gooley JJ, Gaus SE, Saper CB, Lu J (2003) Critical role of dorsomedial hypothalamic nucleus in a wide range of behavioral circadian rhythms. *J Neurosci* 23:10691-10702.
- Coogan AN, Piggins HD (2005) Dark pulse suppression of P-ERK and c-Fos in the hamster suprachiasmatic nuclei. *Eur J Neurosci* 22:158-168.
- Crosio C, Cermakian N, Allis CD, Sassone-Corsi P (2000) Light induces chromatin modification in cells of the mammalian circadian clock. *Nat Neurosci* 3:1241-1247.
- Cuesta M, Clesse D, Pevet P, Challet E (2009) New light on the serotonergic paradox in the rat circadian system. *J Neurochem* 110:231-243.
- Cuesta M, Mendoza J, Clesse D, Pevet P, Challet E (2008) Serotonergic activation potentiates light resetting of the main circadian clock and alters clock gene expression in a diurnal rodent. *Exp Neurol* 210:501-513.



- Curie T, Maret S, Emmenegger Y, Franken P (2015) In Vivo Imaging of the Central and Peripheral Effects of Sleep Deprivation and Suprachiasmatic Nuclei Lesion on PERIOD-2 Protein in Mice. *Sleep* 38:1381-1394.
- Cutrera RA, Kalsbeek A, Pevet P (1993) No triazolam-induced expression of Fos protein in raphe nuclei of the male Syrian hamster. *Brain Res* 602:14-20.
- Cutrera RA, Kalsbeek A, Pevet P (1994) Specific destruction of the serotonergic afferents to the suprachiasmatic nuclei prevents triazolam-induced phase advances of hamster activity rhythms. *Behav Brain Res* 62:21-28.
- Daan S, Pittendrigh CS (1976) Functional analysis of circadian pacemakers in nocturnal rodents.2. Variability of phase response curves. *J Comp Physiol A*:253-266.
- Deboer T (2007) Technologies of sleep research. *Cell Mol Life Sci* 64:1227-1235.
- Deboer T, Vansteensel MJ, Detari L, Meijer JH (2003) Sleep states alter activity of suprachiasmatic nucleus neurons. *Nat Neurosci* 6:1086-1090.
- Deurveilher S, Semba K (2005) Indirect projections from the suprachiasmatic nucleus to major arousal-promoting cell groups in rat: implications for the circadian control of behavioural state. *Neuroscience* 130:165-183.
- Dijk DJ, Beersma DG (1989) Effects of SWS deprivation on subsequent EEG power density and spontaneous sleep duration. *Electroencephalogr Clin Neurophysiol* 72:312-320.
- Dijk DJ, Duffy JF (1999) Circadian regulation of human sleep and age-related changes in its timing, consolidation and EEG characteristics. *Ann Med* 31:130-140.
- Dijk DJ, Shanahan TL, Duffy JF, Ronda JM, Czeisler CA (1997) Variation of electroencephalographic activity during non-rapid eye movement and rapid eye movement sleep with phase of circadian melatonin rhythm in humans. *J Physiol* 505 ( Pt 3):851-858.
- Dudley TE, DiNardo LA, Glass JD (1998) Endogenous regulation of serotonin release in the hamster suprachiasmatic nucleus. *J Neurosci* 18:5045-5052.
- Dudley TE, Dinardo LA, Glass JD (1999) In vivo assessment of the midbrain raphe nuclear regulation of serotonin release in the hamster suprachiasmatic nucleus. *J Neurophysiol* 81:1469-1477.
- Ebihara S, Goto M, Oshima I (1988) The phase-shifting effects of pentobarbital on the circadian rhythm of locomotor activity in the mouse: strain differences. *Brain Res* 454:404-407.
- Edgar DM, Miller JD, Prosser RA, Dean RR, Dement WC (1993) Serotonin and the mammalian circadian system: II. Phase-shifting rat behavioral rhythms with serotonergic agonists. *J Biol Rhythms* 8:17-31.
- Ehlen JC, Paul KN (2009) Regulation of light's action in the mammalian circadian clock: role of the extrasynaptic GABAA receptor. *Am J Physiol Regul Integr Comp Physiol* 296:R1606-1612.
- Ehlen JC, Grossman GH, Glass JD (2001) In vivo resetting of the hamster circadian clock by 5-HT7 receptors in the suprachiasmatic nucleus. *J Neurosci* 21:5351-5357.
- Ehlen JC, Novak CM, Karom MC, Gamble KL, Paul KN, Albers HE (2006) GABAA receptor activation suppresses Period 1 mRNA and Period 2 mRNA in the suprachiasmatic nucleus during the mid-subjective day. *Eur J Neurosci* 23:3328-3336.
- El Allali K, Achaaban MR, Bothorel B, Piro M, Bouaouda H, El Allouchi M, Ouassat M, Malan A, Pevet P (2013) Entrainment of the circadian clock by daily ambient temperature cycles in the camel (*Camelus dromedarius*). *Am J Physiol Regul Integr Comp Physiol* 304:R1044-1052.
- Elliott KJ, Todd Weber E, Rea MA (2001) Adenosine A1 receptors regulate the response of the hamster circadian clock to light. *Eur J Pharmacol* 414:45-53.
- Erhardt C, Galani R, Jeltsch H, Cassel JC, Klosen P, Menet JS, Pevet P, Challet E (2004) Modulation of photic resetting in rats by lesions of projections to the suprachiasmatic nuclei expressing p75 neurotrophin receptor. *Eur J Neurosci* 19:1773-1788.
- Farkas B, Vilagi I, Detari L (2002) Effect of orexin-A on discharge rate of rat suprachiasmatic nucleus neurons in vitro. *Acta Biol Hung* 53:435-443.

- Farsi H, Harti D, Achaaban MR, Piro M, Raverot V, Bothorel B, Ouassat M, Challet E, Pevet P, El Allali K (2020) Melatonin rhythm and other outputs of the master circadian clock in the desert goat (*Capra hircus*) are entrained by daily cycles of ambient temperature. *J Pineal Res* 68:e12634.
- Franken P (2013) A role for clock genes in sleep homeostasis. *Curr Opin Neurobiol* 23:864-872.
- Franken P, Thomason R, Heller HC, O'Hara BF (2007) A non-circadian role for clock-genes in sleep homeostasis: a strain comparison. *BMC Neurosci* 8:87.
- Fukuhara C, Brewer JM, Dirden JC, Bittman EL, Tosini G, Harrington ME (2001) Neuropeptide Y rapidly reduces Period 1 and Period 2 mRNA levels in the hamster suprachiasmatic nucleus. *Neurosci Lett* 314:119-122.
- Gall AJ, Smale L, Yan L, Nunez AA (2013) Lesions of the Intergeniculate Leaflet Lead to a Reorganization in Circadian Regulation and a Reversal in Masking Responses to Photic Stimuli in the Nile Grass Rat. *PLoS One* 8:e67387.
- Gannon RL, Rea MA (1995) Twelve-hour phase shifts of hamster circadian rhythms elicited by voluntary wheel running. *J Biol Rhythms* 10:196-210.
- Gillespie CF, Mintz EM, Marvel CL, Huhman KL, Albers HE (1997) GABA(A) and GABA(B) agonists and antagonists alter the phase-shifting effects of light when microinjected into the suprachiasmatic region. *Brain Res* 759:181-189.
- Glass JD, Tardif SD, Clements R, Mrosovsky N (2001) Photic and nonphotic circadian phase resetting in a diurnal primate, the common marmoset. *Am J Physiol Regul Integr Comp Physiol* 280:R191-197.
- Glass JD, Grossman GH, Farnbauch L, DiNardo L (2003) Midbrain raphe modulation of nonphotic circadian clock resetting and 5-HT release in the mammalian suprachiasmatic nucleus. *J Neurosci* 23:7451-7460.
- Glass JD, Guinn J, Kaur G, Francl JM (2010) On the intrinsic regulation of neuropeptide Y release in the mammalian suprachiasmatic nucleus circadian clock. *Eur J Neurosci* 31:1117-1126.
- Goel N, Lee TM (1997) Social cues modulate free-running circadian activity rhythms in the diurnal rodent, *Octodon degus*. *Am J Physiol* 273:R797-804.
- Golombek DA, Rosenstein RE (2010) Physiology of circadian entrainment. *Physiol Rev* 90:1063-1102.
- Golombek DA, Biello SM, Rendon RA, Harrington ME (1996) Neuropeptide Y phase shifts the circadian clock in vitro via a Y2 receptor. *Neuroreport* 7:1315-1319.
- Goncharuk VD, van Heerikhuize J, Dai JP, Swaab DF, Buijs RM (2001) Neuropeptide changes in the suprachiasmatic nucleus in primary hypertension indicate functional impairment of the biological clock. *J Comp Neurol* 431:320-330.
- Gorman MR, Lee TM (2001) Daily novel wheel running reorganizes and splits hamster circadian activity rhythms. *J Biol Rhythms* 16:541-551.
- Gribkoff VK, Pieschl RL, Wisialowski TA, van den Pol AN, Yocca FD (1998) Phase shifting of circadian rhythms and depression of neuronal activity in the rat suprachiasmatic nucleus by neuropeptide Y: mediation by different receptor subtypes. *J Neurosci* 18:3014-3022.
- Grossman GH, Farnbauch L, Glass JD (2004) Regulation of serotonin release in the Syrian hamster intergeniculate leaflet region. *Neuroreport* 15:103-106.
- Grossman GH, Mistleberger RE, Antle MC, Ehlen JC, Glass JD (2000) Sleep deprivation stimulates serotonin release in the suprachiasmatic nucleus. *Neuroreport* 11:1929-1932.
- Gwinner E (1966a) [On several kinetic plays of the common raven (*Corvus corax* L.)]. *Z Tierpsychol* 23:28-36.
- Gwinner E (1966b) Periodicity of a circadian rhythm in birds by species-specific song cycles (Aves, Fringillidae: *Caeduelis spinus*, *Serinus serinus*). *Experientia* 22:765-766.
- Hannibal J, Ding JM, Chen D, Fahrenkrug J, Larsen PJ, Gillette MU, Mikkelsen JD (1997) Pituitary adenylate cyclase-activating peptide (PACAP) in the retinohypothalamic tract: a potential daytime regulator of the biological clock. *J Neurosci* 17:2637-2644.

- Harrington ME, Schak KM (2000) Neuropeptide Y phase advances the in vitro hamster circadian clock during the subjective day with no effect on phase during the subjective night. *Can J Physiol Pharmacol* 78:87-92.
- Harrington ME, Nance DM, Rusak B (1985) Neuropeptide Y immunoreactivity in the hamster geniculop-suprachiasmatic tract. *Brain Res Bull* 15:465-472.
- Hastings MH, Duffield GE, Smith EJ, Maywood ES, Ebling FJ (1998) Entrainment of the circadian system of mammals by nonphotic cues. *Chronobiol Int* 15:425-445.
- Hattar S, Liao HW, Takao M, Berson DM, Yau KW (2002) Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science* 295:1065-1070.
- Hattar S, Kumar M, Park A, Tong P, Tung J, Yau KW, Berson DM (2006) Central projections of melanopsin-expressing retinal ganglion cells in the mouse. *J Comp Neurol* 497:326-349.
- Herrera CG, Cadavieco MC, Jago S, Ponomarenko A, Korotkova T, Adamantidis A (2016) Hypothalamic feedforward inhibition of thalamocortical network controls arousal and consciousness. *Nat Neurosci* 19:290-298.
- Hickey TL, Spear PD (1976) Retinogeniculate projections in hooded and albino rats: an autoradiographic study. *Exp Brain Res* 24:523-529.
- Horikawa K, Shibata S (2004) Phase-resetting response to (+)8-OH-DPAT, a serotonin 1A/7 receptor agonist, in the mouse in vivo. *Neurosci Lett* 368:130-134.
- Horikawa K, Yokota S, Fuji K, Akiyama M, Moriya T, Okamura H, Shibata S (2000) Nonphotic entrainment by 5-HT1A/7 receptor agonists accompanied by reduced Per1 and Per2 mRNA levels in the suprachiasmatic nuclei. *J Neurosci* 20:5867-5873.
- Hughes AT, Piggins HD (2012) Feedback actions of locomotor activity to the circadian clock. *Prog Brain Res* 199:305-336.
- Huhman KL, Albers HE (1994) Neuropeptide Y microinjected into the suprachiasmatic region phase shifts circadian rhythms in constant darkness. *Peptides* 15:1475-1478.
- Huhman KL, Marvel CL, Gillespie CF, Mintz EM, Albers HE (1997) Tetrodotoxin blocks NPY-induced but not muscimol-induced phase advances of wheel-running activity in Syrian hamsters. *Brain Res* 772:176-180.
- Hut RA, Mrosovsky N, Daan S (1999) Nonphotic entrainment in a diurnal mammal, the European ground squirrel (*Spermophilus citellus*). *J Biol Rhythms* 14:409-419.
- Inouye ST, Kawamura H (1979) Persistence of circadian rhythmicity in a mammalian hypothalamic "island" containing the suprachiasmatic nucleus. *Proc Natl Acad Sci U S A* 76:5962-5966.
- Jacobs BL, Fornal CA (1999) Activity of serotonergic neurons in behaving animals. *Neuropsychopharmacology* 21:9S-15S.
- Janik D, Mrosovsky N (1992) Gene expression in the geniculate induced by a nonphotic circadian phase shifting stimulus. *Neuroreport* 3:575-578.
- Janik D, Mrosovsky N (1993) Nonphotically induced phase shifts of circadian rhythms in the golden hamster: activity-response curves at different ambient temperatures. *Physiol Behav* 53:431-436.
- Janik D, Mrosovsky N (1994) Intergeniculate leaflet lesions and behaviorally-induced shifts of circadian rhythms. *Brain Res* 651:174-182.
- Janik D, Godfrey M, Mrosovsky N (1994) Phase angle changes of photically entrained circadian rhythms following a single nonphotic stimulus. *Physiol Behav* 55:103-107.
- Janik D, Mikkelsen JD, Mrosovsky N (1995) Cellular colocalization of Fos and neuropeptide Y in the intergeniculate leaflet after nonphotic phase-shifting events. *Brain Res* 698:137-145.
- Jha P, Challet E, Kalsbeek A (2015) Circadian rhythms in glucose and lipid metabolism in nocturnal and diurnal mammals. *Mol Cell Endocrinol* 418 Pt 1:74-88.
- Jha PK, Bouaouda H, Gourmelen S, Dumont S, Fuchs F, Goumon Y, Bourgin P, Kalsbeek A, Challet E (2017) Sleep Deprivation and Caffeine Treatment Potentiate Photic Resetting of the Master Circadian Clock in a Diurnal Rodent. *J Neurosci* 37:4343-4358.

- Johnson RF, Smale L, Moore RY, Morin LP (1988) Lateral geniculate lesions block circadian phase-shift responses to a benzodiazepine. *Proc Natl Acad Sci U S A* 85:5301-5304.
- Kalsbeek A, Verhagen LA, Schallij I, Foppen E, Saboureau M, Bothorel B, Buijs RM, Pevet P (2008) Opposite actions of hypothalamic vasopressin on circadian corticosterone rhythm in nocturnal versus diurnal species. *Eur J Neurosci* 27:818-827.
- Kalsbeek A, Palm IF, La Fleur SE, Scheer FA, Perreau-Lenz S, Ruiters M, Kreier F, Cailotto C, Buijs RM (2006) SCN outputs and the hypothalamic balance of life. *J Biol Rhythms* 21:458-469.
- Klisch C, Inyushkin A, Mordel J, Karnas D, Pevet P, Meissl H (2009) Orexin A modulates neuronal activity of the rodent suprachiasmatic nucleus in vitro. *Eur J Neurosci* 30:65-75.
- Ko CH, Takahashi JS (2006) Molecular components of the mammalian circadian clock. *Hum Mol Genet* 15 Spec No 2:R271-277.
- Koletar MM, Cheng HY, Penninger JM, Ralph MR (2011) Loss of *dexras1* alters nonphotic circadian phase shifts and reveals a role for the intergeniculate leaflet (IGL) in gene-targeted mice. *Chronobiol Int* 28:553-562.
- Kornhauser JM, Nelson DE, Mayo KE, Takahashi JS (1990) Photic and circadian regulation of *c-fos* gene expression in the hamster suprachiasmatic nucleus. *Neuron* 5:127-134.
- Lavie P (1997) Melatonin: role in gating nocturnal rise in sleep propensity. *J Biol Rhythms* 12:657-665.
- Lee TM, Labyak SE (1997) Free-running rhythms and light- and dark-pulse phase response curves for diurnal *Octodon degus* (Rodentia). *Am J Physiol* 273:R278-286.
- Liu AC, Welsh DK, Ko CH, Tran HG, Zhang EE, Priest AA, Buhr ED, Singer O, Meeker K, Verma IM, Doyle FJ, 3rd, Takahashi JS, Kay SA (2007) Intercellular coupling confers robustness against mutations in the SCN circadian clock network. *Cell* 129:605-616.
- Liu C, Gillette MU (1996) Cholinergic regulation of the suprachiasmatic nucleus circadian rhythm via a muscarinic mechanism at night. *J Neurosci* 16:744-751.
- Lovenberg TW, Erlander MG, Baron BM, Sutcliffe JG (1993) Cloning of new 5-HT receptors. *Int Clin Psychopharmacol* 8 Suppl 2:19-23.
- Marchant EG, Mistlberger RE (1995) Morphine phase-shifts circadian rhythms in mice: role of behavioural activation. *Neuroreport* 7:209-212.
- Marston OJ, Williams RH, Canal MM, Samuels RE, Upton N, Piggins HD (2008) Circadian and dark-pulse activation of orexin/hypocretin neurons. *Mol Brain* 1:19.
- Maywood ES, Mrosovsky N (2001) A molecular explanation of interactions between photic and non-photic circadian clock-resetting stimuli. *Brain Res Gene Expr Patterns* 1:27-31.
- Maywood ES, Okamura H, Hastings MH (2002) Opposing actions of neuropeptide Y and light on the expression of circadian clock genes in the mouse suprachiasmatic nuclei. *Eur J Neurosci* 15:216-220.
- Maywood ES, Mrosovsky N, Field MD, Hastings MH (1999) Rapid down-regulation of mammalian period genes during behavioral resetting of the circadian clock. *Proc Natl Acad Sci U S A* 96:15211-15216.
- McElroy B, Zakaria A, Glass JD, Prosser RA (2009) Ethanol modulates mammalian circadian clock phase resetting through extrasynaptic GABA receptor activation. *Neuroscience* 164:842-848.
- McGlashan EM, Nandam LS, Vidafar P, Mansfield DR, Rajaratnam SMW, Cain SW (2018) The SSRI citalopram increases the sensitivity of the human circadian system to light in an acute dose. *Psychopharmacology (Berl)* 235:3201-3209.
- McGranaghan PA, Piggins HD (2001) Orexin A-like immunoreactivity in the hypothalamus and thalamus of the Syrian hamster (*Mesocricetus auratus*) and Siberian hamster (*Phodopus sungorus*), with special reference to circadian structures. *Brain Res* 904:234-244.
- Medanic M, Gillette MU (1992) Serotonin regulates the phase of the rat suprachiasmatic circadian pacemaker in vitro only during the subjective day. *J Physiol* 450:629-642.
- Medanic M, Gillette MU (1993) Suprachiasmatic circadian pacemaker of rat shows two windows of sensitivity to neuropeptide Y in vitro. *Brain Res* 620:281-286.

- Meijer JH, Schaap J, Watanabe K, Albus H (1997) Multiunit activity recordings in the suprachiasmatic nuclei: in vivo versus in vitro models. *Brain Res* 753:322-327.
- Meijer JH, Watanabe K, Schaap J, Albus H, Detari L (1998) Light responsiveness of the suprachiasmatic nucleus: long-term multiunit and single-unit recordings in freely moving rats. *J Neurosci* 18:9078-9087.
- Meijer JH, Ruijs AC, Albus H, van de Geest B, Duindam H, Zwinderman AH, Dahan A (2000) Fentanyl, a  $\mu$ -opioid receptor agonist, phase shifts the hamster circadian pacemaker. *Brain Res* 868:135-140.
- Menaker M, Eskin A (1966) Entrainment of circadian rhythms by sound in *Passer domesticus*. *Science* 154:1579-1581.
- Mendoza J, Revel FG, Pevet P, Challet E (2007) Shedding light on circadian clock resetting by dark exposure: differential effects between diurnal and nocturnal rodents. *Eur J Neurosci* 25:3080-3090.
- Mendoza JY, Dardente H, Escobar C, Pevet P, Challet E (2004) Dark pulse resetting of the suprachiasmatic clock in Syrian hamsters: behavioral phase-shifts and clock gene expression. *Neuroscience* 127:529-537.
- Meyer-Bernstein EL, Morin LP (1996) Differential serotonergic innervation of the suprachiasmatic nucleus and the intergeniculate leaflet and its role in circadian rhythm modulation. *J Neurosci* 16:2097-2111.
- Meyer-Spasche A, Reed HE, Piggins HD (2002) Neurotensin phase-shifts the firing rate rhythm of neurons in the rat suprachiasmatic nuclei in vitro. *Eur J Neurosci* 16:339-344.
- Mintz EM, Jasnow AM, Gillespie CF, Huhman KL, Albers HE (2002) GABA interacts with photic signaling in the suprachiasmatic nucleus to regulate circadian phase shifts. *Neuroscience* 109:773-778.
- Mistlberger RE (1991) Effects of daily schedules of forced activity on free-running rhythms in the rat. *J Biol Rhythms* 6:71-80.
- Mistlberger RE, Antle MC (1998) Behavioral inhibition of light-induced circadian phase resetting is phase and serotonin dependent. *Brain Res* 786:31-38.
- Mistlberger RE, Landry GJ, Marchant EG (1997) Sleep deprivation can attenuate light-induced phase shifts of circadian rhythms in hamsters. *Neurosci Lett* 238:5-8.
- Mistlberger RE, Bossert JM, Holmes MM, Marchant EG (1998) Serotonin and feedback effects of behavioral activity on circadian rhythms in mice. *Behav Brain Res* 96:93-99.
- Moore RY, Lenn NJ (1972) A retinohypothalamic projection in the rat. *J Comp Neurol* 146:1-14.
- Moore RY, Speh JC (1993) GABA is the principal neurotransmitter of the circadian system. *Neurosci Lett* 150:112-116.
- Moore RY, Card JP (1994) Intergeniculate leaflet: an anatomically and functionally distinct subdivision of the lateral geniculate complex. *J Comp Neurol* 344:403-430.
- Morin LP (1999) Serotonin and the regulation of mammalian circadian rhythmicity. *Ann Med* 31:12-33.
- Morin LP (2007) SCN organization reconsidered. *J Biol Rhythms* 22:3-13.
- Morin LP (2013) Neuroanatomy of the extended circadian rhythm system. *Exp Neurol* 243:4-20.
- Morin LP, Blanchard J (1995) Organization of the hamster intergeniculate leaflet: NPY and ENK projections to the suprachiasmatic nucleus, intergeniculate leaflet and posterior limitans nucleus. *Vis Neurosci* 12:57-67.
- Morin LP, Blanchard JH (2001) Neuromodulator content of hamster intergeniculate leaflet neurons and their projection to the suprachiasmatic nucleus or visual midbrain. *J Comp Neurol* 437:79-90.
- Morin LP, Allen CN (2006) The circadian visual system, 2005. *Brain Res Rev* 51:1-60.
- Morin LP, Blanchard J, Moore RY (1992) Intergeniculate leaflet and suprachiasmatic nucleus organization and connections in the golden hamster. *Vis Neurosci* 8:219-230.

- Moriya T, Yamanouchi S, Fukushima T, Shimazoe T, Shibata S, Watanabe S (1996) Involvement of 5-HT<sub>1A</sub> receptor mechanisms in the inhibitory effects of methamphetamine on photic responses in the rodent suprachiasmatic nucleus. *Brain Res* 740:261-267.
- Mrosovsky N (1988) Phase response curves for social entrainment. *J comp Physiol A* 162:35-46.
- Mrosovsky N (1996) Locomotor activity and non-photic influences on circadian clocks. *Biol Rev Camb Philos Soc* 71:343-372.
- Mrosovsky N, Salmon PA (1987) A behavioural method for accelerating re-entrainment of rhythms to new light-dark cycles. *Nature* 330:372-373.
- Mrosovsky N, Janik D (1993) Behavioral decoupling of circadian rhythms. *J Biol Rhythms* 8:57-65.
- Mrosovsky N, Edelstein K, Hastings MH, Maywood ES (2001) Cycle of period gene expression in a diurnal mammal (*Spermophilus tridecemlineatus*): implications for nonphotic phase shifting. *J Biol Rhythms* 16:471-478.
- Novak CM, Albers HE (2004) Novel phase-shifting effects of GABA<sub>A</sub> receptor activation in the suprachiasmatic nucleus of a diurnal rodent. *Am J Physiol Regul Integr Comp Physiol* 286:R820-825.
- Novak CM, Ehlen JC, Paul KN, Fukuhara C, Albers HE (2006) Light and GABA (A) receptor activation alter period mRNA levels in the SCN of diurnal Nile grass rats. *Eur J Neurosci* 24:2843-2852.
- Noya SB, Colameo D, Bruning F, Spinnler A, Mircsof D, Opitz L, Mann M, Tyagarajan SK, Robles MS, Brown SA (2019) The forebrain synaptic transcriptome is organized by clocks but its proteome is driven by sleep. *Science* 366.
- Ono M, Watanabe A, Matsumoto Y, Fukushima T, Nishikawa Y, Moriya T, Shibata S, Watanabe S (1996) Methamphetamine modifies the photic entraining responses in the rodent suprachiasmatic nucleus via serotonin release. *Neuroscience* 72:213-224.
- Otalora BB, Hagenauer MH, Rol MA, Madrid JA, Lee TM (2013) Period gene expression in the brain of a dual-phasing rodent, the *Octodon degus*. *J Biol Rhythms* 28:249-261.
- Patton DF, Mistlberger RE (2013) Circadian adaptations to meal timing: neuroendocrine mechanisms. *Front Neurosci* 7:185.
- Pekala D, Blasiak T, Raastad M, Lewandowski MH (2011) The influence of orexins on the firing rate and pattern of rat intergeniculate leaflet neurons--electrophysiological and immunohistological studies. *Eur J Neurosci* 34:1406-1418.
- Pickard GE (1985) Bifurcating axons of retinal ganglion cells terminate in the hypothalamic suprachiasmatic nucleus and the intergeniculate leaflet of the thalamus. *Neurosci Lett* 55:211-217.
- Pickard GE, Ralph MR, Menaker M (1987) The intergeniculate leaflet partially mediates effects of light on circadian rhythms. *J Biol Rhythms* 2:35-56.
- Poncet L, Denoroy L, Jouvet M (1993) Daily variations in in vivo tryptophan hydroxylation and in the contents of serotonin and 5-hydroxyindoleacetic acid in discrete brain areas of the rat. *J Neural Transm Gen Sect* 92:137-150.
- Prosser RA, Gillette MU (1989) The mammalian circadian clock in the suprachiasmatic nuclei is reset in vitro by cAMP. *J Neurosci* 9:1073-1081.
- Prosser RA, Miller JD, Heller HC (1990) A serotonin agonist phase-shifts the circadian clock in the suprachiasmatic nuclei in vitro. *Brain Res* 534:336-339.
- Prosser RA, Heller HC, Miller JD (1994) Serotonergic phase advances of the mammalian circadian clock involve protein kinase A and K<sup>+</sup> channel opening. *Brain Res* 644:67-73.
- Ralph MR, Mrosovsky N (1992) Behavioral inhibition of circadian responses to light. *J Biol Rhythms* 7:353-359.
- Rea MA (1998) Photic entrainment of circadian rhythms in rodents. *Chronobiol Int* 15:395-423.
- Reebs SG, Mrosovsky N (1989a) Large phase-shifts of circadian rhythms caused by induced running in a re-entrainment paradigm: the role of pulse duration and light. *J comp Physiol A* 165:819-825.

- Reebs SG, Mrosovsky N (1989b) Effects of induced wheel running on the circadian activity rhythms of Syrian hamsters: entrainment and phase response curve. *J Biol Rhythms* 4:39-48.
- Reebs SG, Lavery RJ, Mrosovsky N (1989) Running activity mediates the phase-advancing effects of dark pulses on hamster circadian rhythms. *J comp Physiol A* 165:811-818.
- Rensing L, Ruoff P (2002) Temperature effect on entrainment, phase shifting, and amplitude of circadian clocks and its molecular bases. *Chronobiol Int* 19:807-864.
- Ruby CL, Verbanes NM, Palmer KN, Zisk CF, Bunion DJ, Marinos LN (2018) Caffeine Delays Light-entrained Activity and Potentiates Circadian Photic Phase-resetting in Mice. *J Biol Rhythms* 33:523-534.
- Rusak B, Meijer JH, Harrington ME (1989) Hamster circadian rhythms are phase-shifted by electrical stimulation of the geniculate-hypothalamic tract. *Brain Res* 493:283-291.
- Sack RL, Hughes RJ, Edgar DM, Lewy AJ (1997) Sleep-promoting effects of melatonin: at what dose, in whom, under what conditions, and by what mechanisms? *Sleep* 20:908-915.
- Sakurai T (2007) The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. *Nat Rev Neurosci* 8:171-181.
- Saper CB, Fuller PM (2017) Wake-sleep circuitry: an overview. *Curr Opin Neurobiol* 44:186-192.
- Schaap J, Meijer JH (2001) Opposing effects of behavioural activity and light on neurons of the suprachiasmatic nucleus. *Eur J Neurosci* 13:1955-1962.
- Schwartz WJ, Zimmerman P (1990) Circadian timekeeping in BALB/c and C57BL/6 inbred mouse strains. *J Neurosci* 10:3685-3694.
- Sharma VK (2003) Adaptive significance of circadian clocks. *Chronobiol Int* 20:901-919.
- Sharma VK, Chandrashekar MK (1997) Rapid phase resetting of a mammalian circadian rhythm by brief light pulses. *Chronobiol Int* 14:537-548.
- Shibata S, Moore RY (1993) Neuropeptide Y and optic chiasm stimulation affect suprachiasmatic nucleus circadian function in vitro. *Brain Res* 615:95-100.
- Shibata S, Tsuneyoshi A, Hamada T, Tominaga K, Watanabe S (1992) Phase-resetting effect of 8-OH-DPAT, a serotonin<sub>1A</sub> receptor agonist, on the circadian rhythm of firing rate in the rat suprachiasmatic nuclei in vitro. *Brain Res* 582:353-356.
- Shigeyoshi Y, Taguchi K, Yamamoto S, Takekida S, Yan L, Tei H, Moriya T, Shibata S, Loros JJ, Dunlap JC, Okamura H (1997) Light-induced resetting of a mammalian circadian clock is associated with rapid induction of the mPer1 transcript. *Cell* 91:1043-1053.
- Sigworth LA, Rea MA (2003) Adenosine A<sub>1</sub> receptors regulate the response of the mouse circadian clock to light. *Brain Res* 960:246-251.
- Sinclair SV, Mistlberger RE (1997) Scheduled activity reorganizes circadian phase of Syrian hamsters under full and skeleton photoperiods. *Behav Brain Res* 87:127-137.
- Slotten HA, Krekling S, Pevet P (2005) Photic and nonphotic effects on the circadian activity rhythm in the diurnal rodent *Arvicanthis ansorgei*. *Behav Brain Res* 165:91-97.
- Smale L, Lee T, Nunez AA (2003) Mammalian diurnality: some facts and gaps. *J Biol Rhythms* 18:356-366.
- Smale L, Blanchard J, Moore RY, Morin LP (1991) Immunocytochemical characterization of the suprachiasmatic nucleus and the intergeniculate leaflet in the diurnal ground squirrel, *Spermophilus lateralis*. *Brain Res* 563:77-86.
- Smale L, McElhinny T, Nixon J, Gubik B, Rose S (2001) Patterns of wheel running are related to Fos expression in neuropeptide-Y-containing neurons in the intergeniculate leaflet of *Arvicanthis niloticus*. *J Biol Rhythms* 16:163-172.
- Smith RD, Inouye S, Turek FW (1989) Central administration muscimol phase-shifts the mammalian circadian clock. *J Comp Physiol A* 164:805-814.
- Smith RD, Turek FW, Takahashi JS (1992) Two families of phase-response curves characterize the resetting of the hamster circadian clock. *Am J Physiol* 262:R1149-1153.
- Soscia SJ, Harrington ME (2005) Neuropeptide Y does not reset the circadian clock in NPY Y<sub>2</sub><sup>-/-</sup> mice. *Neurosci Lett* 373:175-178.

- St Hilaire MA, Lockley SW (2015) Caffeine does not entrain the circadian clock but improves daytime alertness in blind patients with non-24-hour rhythms. *Sleep Med* 16:800-804.
- Subbaraj R, Chandrashekar M (1978) Pulses of darkness shift the phase of a circadian rhythm in an insectivorous bat. *J Comp Physiol* 127:239-243.
- Sumova A, Maywood ES, Selvage D, Ebling FJ, Hastings MH (1996) Serotonergic antagonists impair arousal-induced phase shifts of the circadian system of the syrian hamster. *Brain Res* 709:88-96.
- Sun ZS, Albrecht U, Zhuchenko O, Bailey J, Eichele G, Lee CC (1997) RIGUI, a putative mammalian ortholog of the *Drosophila* period gene. *Cell* 90:1003-1011.
- Takahashi JS, DeCoursey PJ, Bauman L, Menaker M (1984) Spectral sensitivity of a novel photoreceptive system mediating entrainment of mammalian circadian rhythms. *Nature* 308:186-188.
- Takumi T, Matsubara C, Shigeyoshi Y, Taguchi K, Yagita K, Maebayashi Y, Sakakida Y, Okumura K, Takashima N, Okamura H (1998) A new mammalian period gene predominantly expressed in the suprachiasmatic nucleus. *Genes Cells* 3:167-176.
- Tamaru T, Isojima Y, Yamada T, Okada M, Nagai K, Takamatsu K (2000) Light and glutamate-induced degradation of the circadian oscillating protein BMAL1 during the mammalian clock resetting. *J Neurosci* 20:7525-7530.
- Thomas JM, Kern PA, Bush HM, McQuerry KJ, Black WS, Clasey JL, Pendergast JS (2020) Circadian rhythm phase shifts caused by timed exercise vary with chronotype. *JCI Insight* 5.
- Tobler I, Borbely AA, Groos G (1983) The effect of sleep deprivation on sleep in rats with suprachiasmatic lesions. *Neurosci Lett* 42:49-54.
- Tominaga K, Shibata S, Ueki S, Watanabe S (1992) Effects of 5-HT<sub>1A</sub> receptor agonists on the circadian rhythm of wheel-running activity in hamsters. *Eur J Pharmacol* 214:79-84.
- Tominaga K, Shibata S, Hamada T, Watanabe S (1994) GABA<sub>A</sub> receptor agonist muscimol can reset the phase of neural activity rhythm in the rat suprachiasmatic nucleus in vitro. *Neurosci Lett* 166:81-84.
- Trachsel L, Heller HC, Miller JD (1995) Nicotine phase-advances the circadian neuronal activity rhythm in rat suprachiasmatic nuclei explants. *Neuroscience* 65:797-803.
- Trachsel L, Edgar DM, Seidel WF, Heller HC, Dement WC (1992) Sleep homeostasis in suprachiasmatic nuclei-lesioned rats: effects of sleep deprivation and triazolam administration. *Brain Res* 589:253-261.
- Turek FW (1989) Effects of stimulated physical activity on the circadian pacemaker of vertebrates. *J Biol Rhythms* 4:135-147.
- Turek FW, Losee-Olson S (1986) A benzodiazepine used in the treatment of insomnia phase-shifts the mammalian circadian clock. *Nature* 321:167-168.
- Turek FW, Losee-Olson SH (1987) Dose response curve for the phase-shifting effect of triazolam on the mammalian circadian clock. *Life Sci* 40:1033-1038.
- van Diepen HC, Lucassen EA, Yassenkov R, Groenen I, Ijzerman AP, Meijer JH, Deboer T (2014) Caffeine increases light responsiveness of the mouse circadian pacemaker. *Eur J Neurosci* 40:3504-3511.
- van Oosterhout F, Lucassen EA, Houben T, vanderLeest HT, Antle MC, Meijer JH (2012) Amplitude of the SCN clock enhanced by the behavioral activity rhythm. *PLoS One* 7:e39693.
- Van Reeth O, Sturis J, Byrne MM, Blackman JD, L'Hermite-Baleriaux M, Leproult R, Oliner C, Refetoff S, Turek FW, Van Cauter E (1994) Nocturnal exercise phase delays circadian rhythms of melatonin and thyrotropin secretion in normal men. *Am J Physiol* 266:E964-974.
- Vansteensel MJ, Deboer T, Dahan A, Meijer JH (2003) Differential responses of circadian activity onset and offset following GABA-ergic and opioid receptor activation. *J Biol Rhythms* 18:297-306.
- Vansteensel MJ, Magnone MC, van Oosterhout F, Baeriswyl S, Albrecht U, Albus H, Dahan A, Meijer JH (2005) The opioid fentanyl affects light input, electrical activity and *Per* gene expression in the hamster suprachiasmatic nuclei. *Eur J Neurosci* 21:2958-2966.



- Venner A, Anaclet C, Broadhurst RY, Saper CB, Fuller PM (2016) A Novel Population of Wake-Promoting GABAergic Neurons in the Ventral Lateral Hypothalamus. *Curr Biol* 26:2137-2143.
- Vidal L, Lugo N (2006) Changes in neuropeptide Y immunoreactivity and transcript levels in circadian system structures of the diurnal rodent, the thirteen-lined ground squirrel. *Brain Res* 1125:77-84.
- Vivanco P, Rol MA, Madrid JA (2010a) Temperature cycles trigger nocturnalism in the diurnal homeotherm *Octodon degus*. *Chronobiol Int* 27:517-534.
- Vivanco P, Studholme KM, Morin LP (2013) Drugs that prevent mouse sleep also block light-induced locomotor suppression, circadian rhythm phase shifts and the drop in core temperature. *Neuroscience* 254:98-109.
- Vivanco P, Lopez-Espinoza A, Madariaga AM, Rol MA, Madrid JA (2010b) Nocturnalism induced by scheduled feeding in diurnal *Octodon degus*. *Chronobiol Int* 27:233-250.
- Vyazovskiy VV, Achermann P, Tobler I (2007) Sleep homeostasis in the rat in the light and dark period. *Brain Res Bull* 74:37-44.
- Watanabe A, Moriya T, Nisikawa Y, Araki T, Hamada T, Shibata S, Watanabe S (1996) Adenosine A1-receptor agonist attenuates the light-induced phase shifts and fos expression in vivo and optic nerve stimulation-evoked field potentials in the suprachiasmatic nucleus in vitro. *Brain Res* 740:329-336.
- Webb IC, Pollock MS, Mistlberger RE (2006) Modafinil [2-[(diphenylmethyl)sulfinyl]acetamide] and circadian rhythms in syrian hamsters: assessment of the chronobiotic potential of a novel alerting compound. *J Pharmacol Exp Ther* 317:882-889.
- Webb IC, Antle MC, Mistlberger RE (2014) Regulation of circadian rhythms in mammals by behavioral arousal. *Behav Neurosci* 128:304-325.
- Webb IC, Patton DF, Hamson DK, Mistlberger RE (2008) Neural correlates of arousal-induced circadian clock resetting: hypocretin/orexin and the intergeniculate leaflet. *Eur J Neurosci* 27:828-835.
- Weber ET, Rea MA (1997) Neuropeptide Y blocks light-induced phase advances but not delays of the circadian activity rhythm in hamsters. *Neurosci Lett* 231:159-162.
- Weisgerber D, Redlin U, Mrosovsky N (1997) Lengthening of circadian period in hamsters by novelty-induced wheel running. *Physiol Behav* 62:759-765.
- Wen S, Ma D, Zhao M, Xie L, Wu Q, Gou L, Zhu C, Fan Y, Wang H, Yan J (2020) Spatiotemporal single-cell analysis of gene expression in the mouse suprachiasmatic nucleus. *Nat Neurosci* 23:456-467.
- Werth E, Achermann P, Borbely AA (1996) Brain topography of the human sleep EEG: antero-posterior shifts of spectral power. *Neuroreport* 8:123-127.
- Wever RA (1979) *The circadian system of man. Results of experiments under temporal isolation.* Springer-Verlag: New York, NY.
- Wickland C, Turek FW (1994) Lesions of the thalamic intergeniculate leaflet block activity-induced phase shifts in the circadian activity rhythm of the golden hamster. *Brain Res* 660:293-300.
- Wickland CR, Turek FW (1991) Phase-shifting effects of acute increases in activity on circadian locomotor rhythms in hamsters. *Am J Physiol* 261:R1109-1117.
- Wright KP, Jr., Badia P, Myers BL, Plenzler SC, Hakel M (1997) Caffeine and light effects on nighttime melatonin and temperature levels in sleep-deprived humans. *Brain Res* 747:78-84.
- Yamada N, Shimoda K, Takahashi K, Takahashi S (1986) Change in period of free-running rhythms determined by two different tools in blinded rats. *Physiol Behav* 36:357-362.
- Yamakawa GR, Basu P, Cortese F, MacDonnell J, Whalley D, Smith VM, Antle MC (2016) The cholinergic forebrain arousal system acts directly on the circadian pacemaker. *Proc Natl Acad Sci U S A* 113:13498-13503.
- Yamazaki S, Kerbeshian MC, Hocker CG, Block GD, Menaker M (1998) Rhythmic properties of the hamster suprachiasmatic nucleus in vivo. *J Neurosci* 18:10709-10723.
- Youngstedt SD, Elliott JA, Kripke DF (2019) Human circadian phase-response curves for exercise. *J Physiol* 597:2253-2268.

**Fig. 1.** Temporal organization of daily rhythms of (A) sleep, (B) body temperature, (C) blood glucose and (D) plasma glucocorticoids in nocturnal (blue line) and diurnal (red line) mammals.

**Fig. 2.** Schematic representation of effects of light-induced phase shifts in nocturnal and diurnal mammals housed in constant darkness. (A-B) Actograms of wheel-running activity of nocturnal (A) and diurnal (B) rodents. Yellow circles represent time-points of brief light exposure. (C-D) Phase-response curves to light in nocturnal (C) and (D) diurnal animals.

**Fig. 3.** Schematic network of brain nuclei and neurotransmitters involved in photic and non-photic entrainments. Photic signals transmitted to the SCN directly via RHT releasing glutamate and PACAP. Non-photic signals utilize network of neural connections involving DR and MR, the IGL, BF and the LH to reach the SCN. These networks use serotonin, NPY, GABA, enkephalin, neurotensin, acetylcholine and orexin to transmit arousal-related information to the SCN. BF, basal forebrain; DR, dorsal raphe; Enk, enkephalin; GABA, gamma amino butyric acid; GHT, geniculohypothalamic tract; Glu, glutamate; IGL, intergeniculate leaflet; LH, lateral hypothalamic area; MR, median raphe; Neur, neurotensin; PACAP, pituitary adenylate-cyclase-activating peptide; RHT, retinohypothalamic tract; SCN, suprachiasmatic nucleus..

**Fig. 4.** Schematic representation of phase-shifts induced by sleep deprivation (SD), light pulse and a combination of both for nocturnal and diurnal mammals kept in constant darkness. (A-B) Actograms of wheel-running activity of nocturnal (A) and diurnal (B) rodents. Gray rectangular bars represents timelines of sleep deprivation and yellow circles represent time-points of brief light exposure. Phase advances and delays are represented by positive and negative signs, respectively.

**Figure 1**

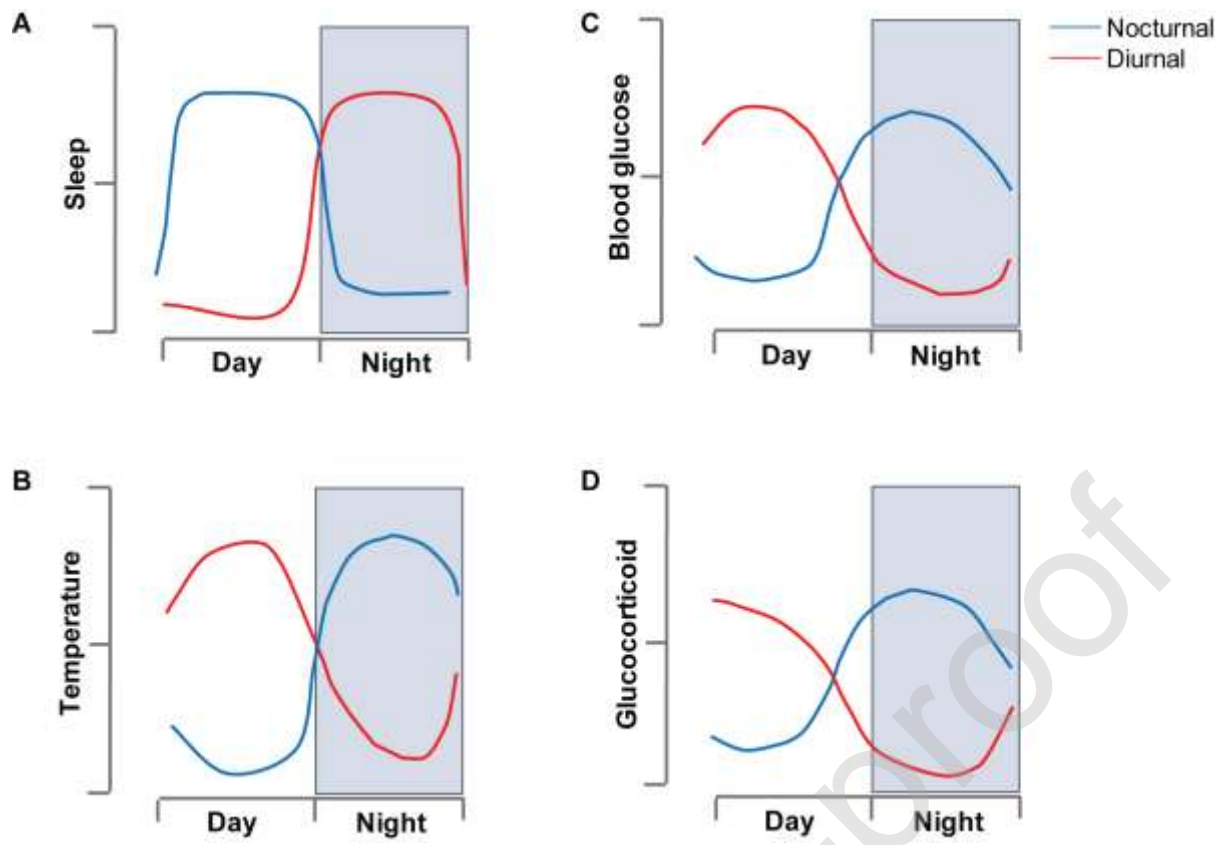


Figure 2

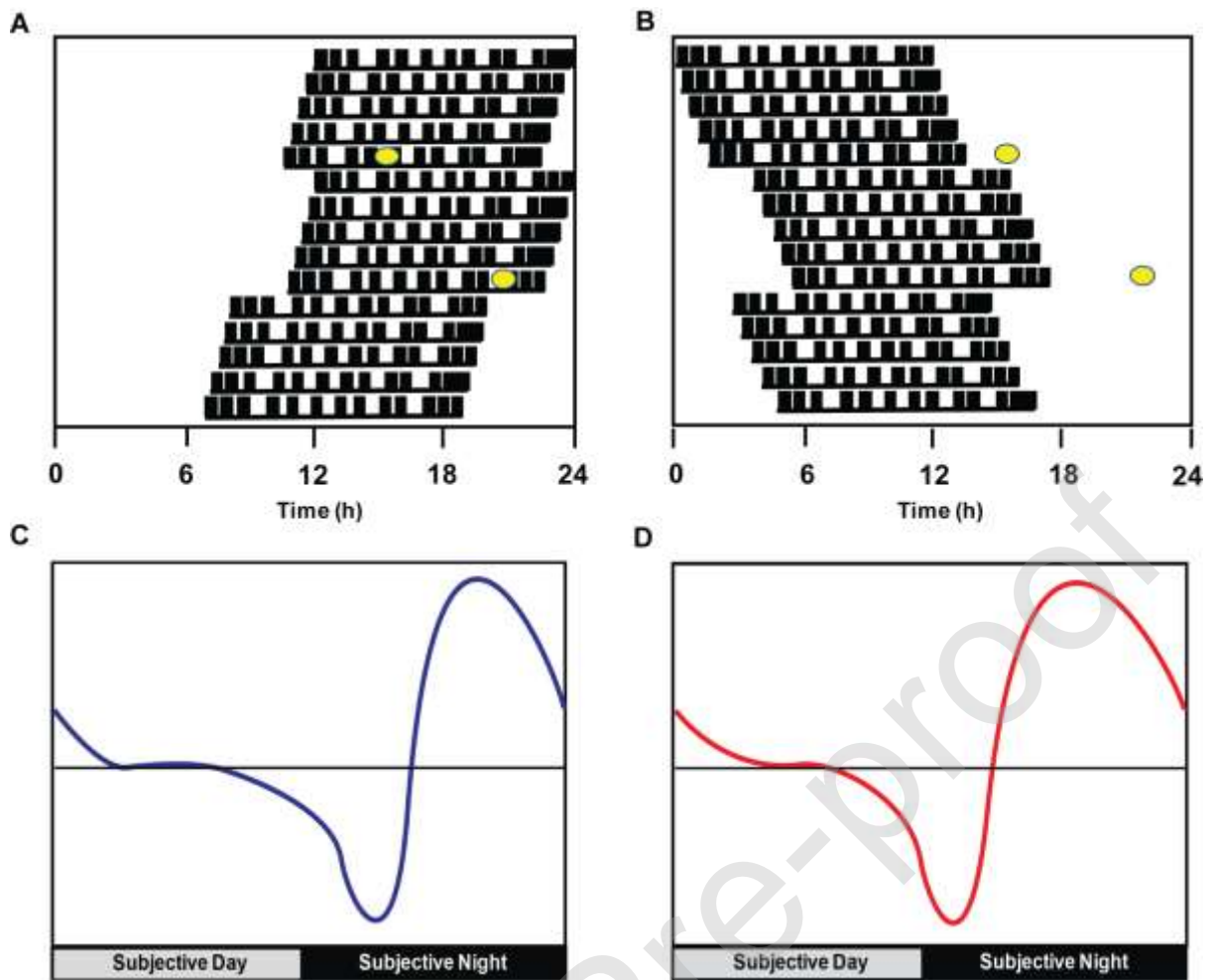


Figure 3

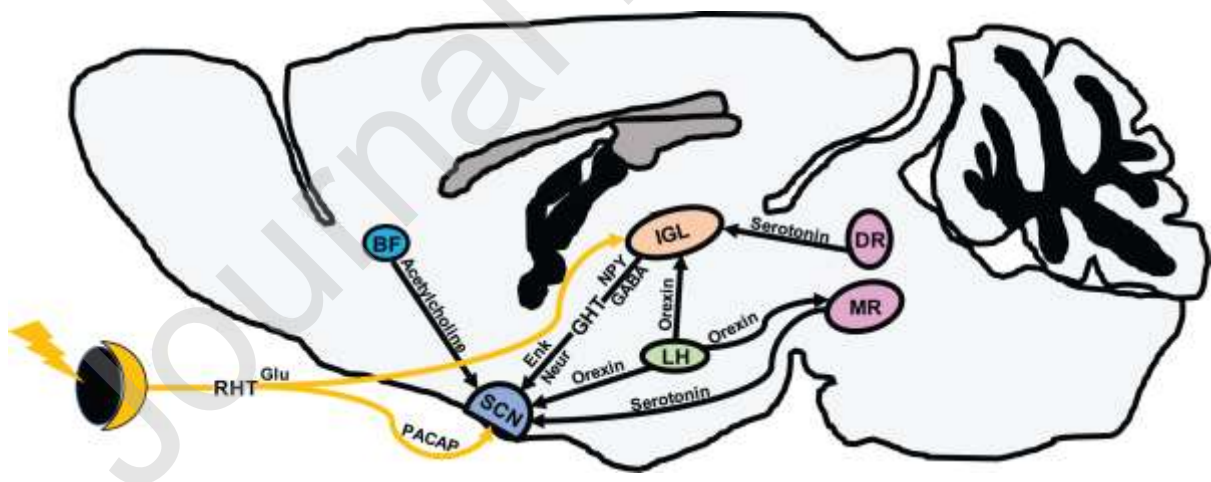
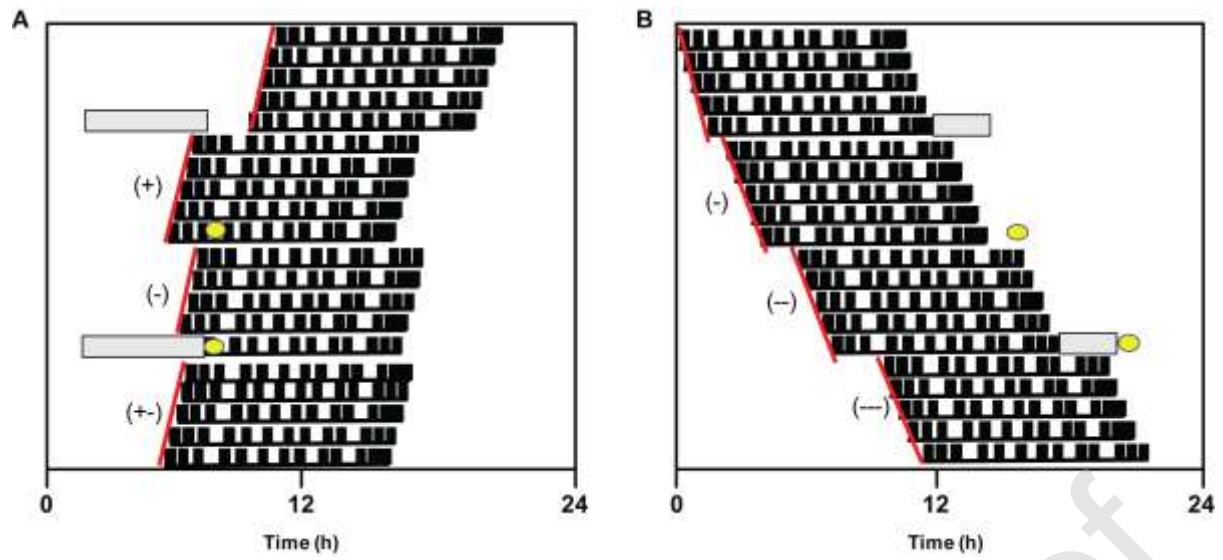


Figure 4



Journal Pre-proof