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

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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; Otolara 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. Photoc entrainment may influence, and be influenced by, the non-photoc phase resetting in mammals. Therefore, we must first discuss photoc 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 photoc information to the SCN (Moore and Lenn, 1972). It is now well established that photoc 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 chromatic 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; Reeb 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, *Tapozous 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 caused 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-photic 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-photic 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_A receptor agonists have been shown to perturb the circadian phase in hamsters and mice. Midday central administration of the GABA_A 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-photic like phase-shifts in rest-activity and SCN electrical activity rhythms (Tominaga et al., 1994; McElroy et al., 2009). SCN GABA_A 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_A 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_A 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 μ 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_{1,2,7} and 5-HT₇ 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_{1A/7} 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-photic 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-photic 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-photic stimuli such as systemic injections of 5-HT_{1A/7} 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-HT₇ and 5-HT_{1A} receptors (Lovenberg et al., 1993; Cuesta et al., 2009). Activation of 5-HT₇ 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-photic 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_{1A} agonist can be inhibited by pretreatment of the slice with a PKA inhibitor (Prosser et al., 1994). The non-photic-like phase-shift induced by NPY is mediated by the NPY Y₂ 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 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 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.

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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, γ -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