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Regulation of circadian physiology and behavior by light in mammals: entrainment and masking

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Author contributions

Jia-Min Liu, Ya-Min Yang, Wei Xu and Xiao-Dong Li discussed and conceived this work; Xiao-Dong Li wrote the manuscript, Jia-Min Liu, Ya-Min Yang and Wei Xu provided feedback during the writing.

Competing interests

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Abbreviations

Tb, body temperature; LD, light/dark; DD, constant darkness; SCN, suprachiasmatic nucleus; RGCs, retinal ganglion cells; OPN4, melanopsin; IPL, inner plexiform layer; PRC, phase response curve; IGL, intergeniculate leaflet; VTA, ventral tegmental area; SPZ, subparaventricular zone; FAA, food anticipatory activity; FEO, food entrainable oscillator; BNST, bed nucleus of stria terminalis; PLR, pupillary light reflex; SC, superior colliculus.

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Abstract

Both entrainment and the direct effects of light are critically involved in the overt manifestation of circadian rhythms. The modern use of electric lights alters environmental lighting, leading to light exposure at inappropriate times to disturb circadian homeostasis for both human and wildlife. The light "pollution" and voluntary activities such as night shift work and transmeridian travelling have adverse consequences such as mood and metabolic disorders in humans. On the other hand, insufficient light exposure decreases neurotransmission from the locus ceruleus and dorsal raphe, leading to seasonal and nonseasonal affective disorders, while properly timed bright light is beneficial to mood and cognition. Given the critical and complex roles of light in mammalian physiology and behavior, it is essential to understand the underlying mechanisms. In this review, we discuss the neural mechanisms through which light regulates and dysregulates circadian rhythms in mammals.

Keywords: light, circadian rhythms, mammal

Introduction

Earth's self-rotation around its own axis results in the daily alternation of light and darkness, and its orbiting around the sun leads to changes in day length across the year. Daily and seasonal changes in physiology and behavior are evident in many organisms [1]. In mammals, melatonin and glucocorticoid levels are known to fluctuate across the day. In addition, feeding, locomotor activity, body temperature (Tb) and sleep all exhibit rhythmic daily changes. Those rhythms are called circadian rhythms, since they are not simply imposed by the external light/dark (LD) cycle but persist under constant darkness (DD), albeit with periods slightly different from 24 h. Light adjusts clock phase and period to match that of the LD cycle, a process termed entrainment [2–5]. Light also exerts direct impact on mammalian physiology and behavior. For example, light suppresses melatonin synthesis at night in rodents and man [6, 7]. The direct effects of light, also called the "masking" effects , could be independent of entrainment and may mask the true state of clock oscillation [8, 9].

Both entrainment and the direct effects of light are involved in the overt manifestation of circadian rhythms. The modern use of electric lights alters environmental illuminance, leading to light exposure at inappropriate times to disturb circadian homeostasis for both human and wildlife [10–12]. Light "pollution" and voluntary activities such as night shift work and transmeridian travelling have adverse consequences such as mood and metabolic disorders in humans [10, 13]. On the other hand, insufficient light exposure decreases neurotransmission from the locus ceruleus and dorsal raphe, leading to seasonal and non-seasonal affective disorders, while properly timed bright light is beneficial to mood and cognition in animals and humans [14–17]. Given the critical and complex roles of light in mammalian physiology and behavior, it is essential to understand the underlying mechanisms. In this review, we discuss the neural mechanisms by which light regulates and dysregulates circadian rhythms in mammals and the limitations of current research. The practical use of this knowledge to benefit health is also discussed.

The circadian timing system in mammals

The neural basis of circadian timing has been extensively characterized during the past 50 years after the suprachiasmatic nucleus (SCN) is identified as the central pacemaker in mammals in 1972 [18]. Moreover, the molecular basis of circadian timing is unraveled [19, 20]. Most mammalian cells possess endogenous clocks that orchestrate cell-specific gene expression rhythms and physiological functions. The molecular clock controls the rhythm of SCN neural activity that serves as SCN output to downstream targets [21]. The SCN regulates sympathetic input to the pineal gland and rhythmic melatonin synthesis [22–24]. The seasonal changes in photoperiod (i.e., duration of light per day) have tremendous impact on daily melatonin production and reproductive activities [25]. The SCN controls the glucocorticoid rhythm through dual routes: control over the HPA axis (i.e., pituitary ACTH secretion) and control over sympathetic input to the adrenal gland [26]. In addition, the adrenal gland possesses an endogenous clock to gate its responsiveness to circulating ACTH [27]. The SCN also regulates neuroendocrine rhythms related to the estrous cycle [28]. The activity rhythm is also readout of SCN output. General activity can be monitored via infrared motion detectors or implanted E-mitters. Alternatively, the animal is given a wheel to monitor its wheel-running. The SCN exerts control over sleep, which is also regulated by homeostatic and motivational mechanisms [29–33]. In humans living without time cues, the sleep rhythm can be uncoupled from other clock- controlled rhythms (e.g., Tb rhythm), a phenomenon called "internal desynchronization" [34, 35].

The SCN receives photic cues via the retinohypothalamic tract (RHT), which arises from retinal ganglion cells (RGCs) that express the photopigment melanopsin (OPN4). Those RGCs are intrinsically photosensitive (ipRGCs) via phototransduction by OPN4, and they also receive rod and cone inputs via bipolar and amacrine cells [36–40]. Currently, ipRGCs in mammals are classified into six types according to differences in somadendritic morphology and location relative to the inner plexiform layer (IPL) of the retina [41]. They also markedly differ in OPN4 expression levels and projection targets [41]. In adult animals, the intrinsic photic responses appear significant in the M1 and M2 types, while other types are mainly driven by rod/cone inputs. The SCN receives M1&2 inputs. Two distinct albeit complimentary theories are proposed for the mechanism of clock entrainment by light [2–4, 42]. Parametric entrainment emphasizes light's continuous modulation over the clock's angular velocity to adjust its phase and period, while nonparametric entrainment emphasizes the discrete effects of brief light pulses to abruptly phase shift the clock [43]. The magnitude of the phase shift by a light pulse varies across the day and with photic history, and the phase response curve (PRC) is characterized by a daytime dead zone, an early night phase-delay zone, and a late night phase-advance zone [44–46]. The thalamic intergeniculate leaflet (IGL) also receives light input and conveys photic cues via the geniculohypothalamic tract to the SCN [47]. Neurotoxic IGL lesion in Syrian hamsters flattens the PRC, leading to defects in re-entrainment when the LD cycle is abruptly changed [48]. The SCN and IGL have converging hypothalamic projections and cooperate to control circadian rhythms[49].

Nonphotic cues (e.g., regularly scheduled voluntary exercise) can also entrain the SCN clock. The IGL interconnects with brain areas related to arousal, visuomotor and vestibular functions [50–53]. Activity induced during rest by a novel wheel activates NPY neurons in the IGL and elicits phase advance in the SCN [54–56]. Temperature is a weak nonphotic cue whose entraining effect relies on locomotor activity in response to temperature changes [57, 58]. Besides NPY input from the IGL, the SCN also receives nonphotic inputs from serotonin neurons of the median raphe and dopamine neurons of the ventral tegmental area (VTA) [59, 60]. The photic and nonphotic inputs to the IGL and SCN are mutually antagonistic [47, 61]. In the IGL, light activates ENK neurons to inhibit NPY neurons [62, 63]. IGL NPY neurons, probably assisted by serotoninergic inputs to the IGL and SCN, oppose SCN's activation by light [56, 64, 65].

The temporal niche and flexibility in circadian timing: the SCN and the extra-SCN oscillators

The daily timing of activity, temporal niche in ecological terms, is critical for animals to obtain sufficient food and avoid predators [66]. There is diversity of temporal niches in mammals [67]. While certain species are active at crepuscular times, diurnal species are mainly active during the light phase of the LD cycle, whereas nocturnal animals spend more time asleep during the day and are mainly active during darkness at night. The daily rhythms of activity, feeding, drinking, Tb, and peripheral clocks are all phase-reversed between diurnal and nocturnal animals [68]. The glucocorticoid rhythm peaks near activity onset in both diurnal and nocturnal species, thus is also phase-reversed. However, the melatonin rhythm peaks at night in both diurnal and nocturnal animals [24].

Despite the phase reversals of most overt rhythms, the SCN is similarly entrained to the LD cycle in diurnal and nocturnal animals, as evidenced by its daily activation and clock protein expression [69]. On the other hand, population neural activity in the subparaventricular zone (SPZ), an area above the SCN, is antiphasic to that in the SCN in nocturnal animals but in phase with the SCN in diurnal animals. The SPZ is suggested to be a relay where SCN output reverses its sign in diurnal animals [69]. Using cFOS and clock proteins as markers, it was shown that the lower SPZ (LSPZ) is activated in a largely antiphasic manner to the SCN in the diurnal Nile grass rats (*Arvicanthis niloticus*) under the LD cycle and DD, likely due to inhibition of the LSPZ by SCN output [70, 71]. By contrast, in nocturnal animals under LD (but not after prolonged DD), LSPZ is activated in phase with the SCN, a pattern suggested to be due to retinal inputs to the LSPZ that counter inhibition by the SCN [70, 72, 73]. However, light at night induce c-FOS in the LSPZ of both Nile

grass rats and most nocturnal animals [74]. Moreover, the overall effect of light in the SPZ of nocturnal animals such as mice appears to be inhibitorty, most probably owing to inhibition by the SCN [71, 75]. Besides the RHT and SCN, the SPZ receives inputs from other sources, and its neural activity is closely related to locomotor activity and may exert control over the SCN in return [71, 75–78]. The identity of LSPZ neurons activated across the day and by light and their afferent and efferent connections remain to be fully characterized. LSPZ lesion weakens without abolishing or phase-reversing the behavioral rhythm, suggesting that other areas than the LSPZ are also involved in phase-reversing SCN output [79–81].

Brain regions that receive SCN input (or not) could also be influenced by other neural inputs. Engagement of those regions can reprogram overt circadian rhythms according to physiological needs [82]. For example, restricting food access to a fixed time window induces anticipatory activity to food (FAA) in both intact and SCN-lesioned animals [83]. The FAA, including increases in locomotor activity, Tb, and glucocorticoid, is driven by the so-called food entrainable oscillator (FEO). Food shortage and/or low ambient temperature also render nocturnal animals active during day time, while their SCN clocks remain phase-locked to the LD cycle [84]. The limbic areas are involved in learning and memory as well as reward and motivation. Notably, limbic areas such as the bed nucleus of stria terminalis (BNST), amygdala (BLA and CEA), striatum, and hippocampus express clock proteins, and the expression is entrained by scheduled feeding [85]. Scheduled feeding is also a powerful cue to entrain peripheral clocks but not the SCN [86–88].

VTA dopamine neurons play essential roles in reward and motivation [33]. Methamphetamine increases dopaminergic neurotransmission. Similar to the FEO, a methamphetamine-sensitive circadian oscillator can also coordinate overt rhythms and peripheral clocks in intact and SCN-lesioned animals [89–91]. Reward and motivation mechanisms are intimately involved in wheel-running (but not general activity) [92]. Interestingly, when diurnal animals are given access to the running wheel, some prefer to run on the wheel during darkness and rapidly become night-active, while others remain day-active [93, 94]. The SCN in day- and night-active animals is similarly entrained to the LD cycle, as evidenced by the temporal expression of clock genes [95]. Daily LSPZ activation is also unaltered, suggesting that it does not mediate the behavioral phase-reversal [95]. However, the clock protein rhythms in limbic areas, which depend on both the glucocorticoid rhythm and SCN input , tend to be phase reversed [95, 96]. This suggests that the glucocorticoid rhythm also markedly differs between the two chronotypes.

Roles of entrainment and direct effects of light in physiology and behavior

The temporal niche and flexibility in circadian timing enable the organism to adapt to environmental changes and maximize survival. Light is arguably the most important ecological factor to determine an organism's temporal niche. The phase angle of entrainment controls phasing of the activity-rest rhythm to the LD cycle, giving rise to chronotypes such as "morning larks" and "night owls" in humans [97]. Individuals with shorter clock periods (e.g., those bearing the hPER2 S662G mutation) tend to have an advanced phase angel of entrainment and go to bed early at night and wake up early in the morning [98]. The direct effects of light on activity and sleep/wake state cooperate with entrainment to determine the temporal niche [99]. In diurnal animals, the dominant effect of light at various intensities is to increase locomotion [100]. In nocturnal animals, low-intensity light promotes activity, an effect termed "positive masking" and mediated by the classical image forming visual system (e.g., the dorsolateral geniculate and visual cortex) [9, 101, 102]. However, light at relatively high intensities inhibits locomotor activity and promotes sleep in nocturnal rodents, an effect termed "negative masking". Both negative masking and clock phase-shifting by light depend on the integrity of M1 ipRGC functions [38, 39, 103–105]. Since ipRGCs integrate intrinsic OPN4 signaling and rod/cone inputs, their activation is influenced by light's spectral composition and duration as well as its intensity [40, 106]. Rod contributes to M1 ipRGC activation at both scotopic and photopic light levels [107, 108]. The S-cones and intrinsic OPN4 signaling have much slower light adaptation kinetics than the M-cones, and both significantly contribute to M1 ipRGC activation at high light intensities. By contrast, the M-cones only make brief contribution at the initial stage of mesopic/photopic light detection [40, 109].

A once prevailing view is that light affects physiology and behavior via regulating the SCN clock, which is revised after the discovery of ipRGCs and their extra-SCN targets [13, 110, 111]. While entrainment has been well studied and is fairly understood, the direct actions of light on the SCN and extra-SCN regions are the focus of recent studies. Below we review the historical development on elucidating the neural mechanisms for the direct effects of light. While many mechanistic studies cited are done in rodents, human studies are discussed when relevant. We start with nocturnal rodents, focusing on light's negative effects on wakefulness and locomotion. In the last part of this review, we discuss the mechanism (s) for the dominance of positive masking in diurnal animals.

The negative masking effect of light is accompanied with a phase shift of the SCN clock in nocturnal animals

Because the acute effect of light on behavior is typically accompanied with a phase shift of the SCN clock that potentially resets the clock output mode to the daytime domain, a prevailing view is that SCN serves as a critical structure that mediate the negative masking effect of light on locomotor activity in nocturnal animals [7]. This view is supported by Prof. DeCoursey's 1986 study on the flying squirrel (*Glaucomys volans*) under semi-natural condition [112]. Pat DeCoursey housed those nocturnal rodents individually in simulated den cages (nest boxes without light exposure) that are connected to the activity room via a darkened tunnel. Food and running-wheel are available in the activity room, where a LD cycle is also imposed. At its nocturnal activity onset, the flying squirrel would come out its den and proceeds quickly through the tunnel. Near the tunnel exit, if the animal encounters bright light from the activity room, it stays immobile at the porthole for a brief period (seconds to minutes). After this "light-sampling", it would return to the nest box for a brief nap (typically less than an hour), then re-emerges to repeat the light-sampling routine. When darkness is finally met, the animal would rapidly enter the activity room and engage in wheel-running and other activities. The brief light exposure at the porthole causes a permanent phase delay of the animal's clock, as evidenced by the onsets of wheel-running on the day of light exposure and the following days. Moreover, the magnitude of the phase delay is equal to the duration of the rest after light-sampling [112]. This suggests that light instantaneously delays the SCN clock, and the nonparametric phase change leads to an increase of SCN neural activity to daytime levels, accounting for the nap after light-sampling.

The wheel-running behavior is often employed in laboratory studies of masking, with the wheel equipped in the animal's home cage. This behavioral assay reveals robust negative masking effect of light at night, when nocturnal rodents are active. Light exposure for 5 min, or light flashes lasting for only 20 ms in total over 5 min, is sufficient to inhibit wheel-running in mice for a prolonged period [113]. The initial 10 min after light onset is characterized by a decrease in wheel-running and general activity (behavioral quiescence), followed by behavioral sleep for about 25 min. The effect of light to inhibit locomotion and induce sleep is termed "photosomnolence" [113, 114].

While the above results support a role of phase resetting in the behavioral manifestation of negative masking, in-depth investigation revealed differences between the two effects of light. Firstly, the negative masking effect is additive: increasing the light pulse duration sustains behavioral inhibition well after the phase-shifting effect is saturated [115]. Thus, the duration of behavioral inhibition does not correlate well with the phase shift magnitude. Secondly, light-induced phase change takes 1–2 h to complete [43]: for two light pulses to add

up their phase-shifting effects in the SCN, they must be separated by at least one hour [116]. Thus, phase resetting is probably too slow to fully account for the rapid (in just a few minutes) induction of photosomnolence.

The phase-shifting and negative masking effects of light can be dissociated

Additional evidence supports the view that negative masking involves mechanism(s) in addition to phase-shifting the SCN. First of all, behavioral inhibition by light could be graded, a phenomenon not easily accounted for by an abrupt phase shift of the SCN clock. At the appropriate light intensity, a mere 50% inhibition of wheel-running could be achieved in WT animals [117]. Moreover, mutations can impair masking but not phase-shifting. For example, the *Waved-2* mice bear a hypomorphic mutation in the EGF receptor gene [118]. Compared to WT mice, the mutants expand their activity duration under LD (but not DD) by exhibiting more wheel-running during the hours before light-off and after light-on [118]. During hours' light at night that elicits normal phase shifts in the mutants, wheel-running also persists (albeit at about 50% of baseline) in them [118]. Overall, light (at least at certain intensities) does not appear to initiate and maintain complete behavioral quiescence in the mutants [119]. The graded masking responses probably are unnatural in that the animals have no escape from light, thus might be seen only under laboratory conditions. Nonetheless, they indicate that the negative masking and phase-shifting effects of light could be dissociated. Such dissociation, while compatible with nonparametric entrainment with "transients" of slower kinetics, is also consistent with parametric entrainment by light, i.e., slowing down the clock's speed rather than abruptly shifting its phase.

Negative masking can even take place without phase-shifting the SCN. For example, a mouse strain exhibits no signs of entrainment to the LD cycle, but its wheel-running is still inhibited by light [120]. In arrhythmic clock mutant mice, negative masking remains normal or slightly impaired due to pleiotropic effects of the mutations [121, 122]. Negative masking is also evident under short LD cycles, which exert parametric effects on clock period without disrupting the activity rhythm [123]. Mice avoid running on the wheel during the light phase of the short LD cycle (e.g., 3.5 h:3.5 h) [39]. In albino rats exposed to short LD cycles, light acutely promotes NREM sleep while darkness promotes REM sleep [124]. In mice under short LD cycles, the REM-sleep enhancing effect of darkness persists , but the direct effect of light on NREM sleep may not always be evident [125–128]. Nonetheless, for mice under a normal LD cycle, light clearly promotes NREM sleep at early night, while darkness promotes wakefulness at early day [129, 130].

Role of the SCN in photosomnolence in nocturnal rodents

The dissociation of negative masking from phase-shifting suggests that the two effects of light could be mediated by distinct mechanisms. However, this does not exclude the SCN from participating in negative masking. Lesion studies support a role of the SCN in negative masking. After the RHT connection to SCN is severed (leaving retinal input to other areas largely intact) in Syrian hamsters, the hamsters still remain rhythmic but fail to entrain or diminish wheel-running by light [131]. SCN lesion severely disrupts negative masking in Syrian hamsters , although this result is contradicted by that of another study [132, 133]. The discrepancy could be due to the electrolytic lesion approach used in both studies, which inevitably damages retinal input to the SPZ (and possibly other regions), with potential damage to the SPZ itself. The extent of such damages may vary among studies, leading to variability in results [132].

In nocturnal rodents, the SCN promotes sleep during day time, when its neural activity peaks [29]. The SCN is also postulated to play a critical role in sleep induction by light [7, 134]. This conjecture is corroborated by a recent study showing that the SCN mediates 77% of the photosomnolence effect in mice through both circadian and clock-independent mechanisms [135]. Firstly, light elicits excitatory responses in the SCN of nocturnal animals, thus boosting the clock role of SCN in sleep regulation via increasing circadian amplitude [135–137]. Secondly, while neuronal membrane depolarization can be linked to SCN clock entrainment, SCN neurons activated by light can relay light signals to downstream targets without the need to be intrinsically rhythmic [5, 7, 21, 135]. Indeed, in WT animals, not all SCN neurons receiving retinal input possess endogenous clocks [138]. A non-clock role of SCN in masking is self-evident in arrhythmic clock mutant mice [71].

Light also acts on the SCN region to increase glucocorticoid, leading one study to claim that light activates the SCN to promote wakefulness only [26, 139–141]. This oversimplified view deserves scrutiny. Glucocorticoid stabilizes central and peripheral clocks against phase disturbance by light, and its induction by light is likely similar in nocturnal rodents and man, albeit with conflicting results in human studies [26, 139, 142–146]. However, while the SCN region is implicated in increasing glucocorticoid by light, a role for retinal input bypassing the SCN to nearby structures (e.g., SPZ) could not be ruled out [26]. Even if some SCN neurons serve as the conduit for light to impact on adrenal functions, the SCN can still regulate sleep via its other neurons.

Extra-SCN structures mediating photosomnolence in nocturnal rodents

The M1 ipRGCs are critically involved in photosomnolence, and they project to the SCN and multiple extra-SCN areas such as the IGL, ventrolateral preoptic nucleus (VLPO) of the hypothalamus, lateral habenula (LHb) and the parahabenula region (PHb) [147, 148]. M1 ipRGCs are divided into two subtypes based on Brn3b expression [103, 104]. Brn3b$^+$ M1 ipRGCs innervate the VLPO, which is involved in sleep regulation [149]. While retinal fibers in VLPO are sparse relative to those in the SCN and IGL, their optogenetic activation induces sleep in mice [149]. A caveat to note is that Brn3b$^+$ M1 ipRGCs project to VLPO as well as other structures (e.g., the SCN and IGL) [103, 104]. Stimulating the retinal fibers in VLPO may antidromically activate Brn3b$^+$ M1 ipRGCs that send collaterals to the IGL and/or SCN. Previous studies showed that IGL lesion increases negative masking in hamsters and has no effect on light-induced Tb reduction in rats [150, 151]. However, electrolytic lesion may damage retinal fibers of passage and impair positive masking mediated by the DLG, obscuring IGL's role in negative masking. Indeed, genetic ablation of GABAergic neurons in the IGL attenuates photosomnolence in mice [101, 129]. One study found that photosomnolence in mice is abolished after ablating the Brn3b$^+$ ipRGCs [147]. Examination of its results (Figure 2D–2G , 4D–4G of [147]), however, reveals residual light responses (about 50% relative to WT mice during the 1st hour after light onset). Thus, the Brn3b$^-$ipRGCs, which project to the SCN and IGL103, may also contribute to photosomnolence.

The IGL, its adjacent ventrolateral geniculate (VLG), and retinorecipient areas in the pretectum and midbrain are interconnected, and those structures are collectively called the subcortical visual shell (SVS) [152]. SVS structures receive inputs from multiple ipRGC types and conventional RGCs [153, 154], and they possess endogenous clocks and neural rhythms that can be entrained by light [155]. As the hub of the SVS, the IGL/VLG projects to brain areas related to behavioral state control in addition to visuomotor functions [51, 53]. The SVS and SCN form the "circadian visual system" to regulate circadian rhythms and behavioral states [47]. Most neurons in the IGL/VLG are GABAergic, but they come from two lineages: *Sox14*$^+$*/Dlx1,2*$^-$ and *Sox14*$^-$*/Dlx1,2*$^+$ precursors [156]. Their neurochemical heterogeneity remains to be fully characterized. The *Sox14*$^+$ neurons, some of which express NPY, do not receive M1 ipRGC input [157]. In *Sox14* KO mice, NPY neurons over-accumulate in the IGL [156]. The mutants exhibit normal rhythms under DD, normal c-FOS induction in the SCN by light, and a normal pupillary light reflex (PLR). However, they are less sensitive to the entraining and negative masking effects of light. Under LD, the mutants begin activity well before light-off, and nearly half of their daily activity occurs in the light phase. Light also fails to inhibit their activity at night [156]. The deficit in negative masking is consistent

with the roles of NPY in arousal and antagonizing light input to the SCN [61]. By contrast, ENK neurons in the IGL/VLG, which probably are of the Sox14$^-$ type and receive M1 ipRGC input, likely plays a critical role in photosomnolence.

During development, some IGL neurons migrate to other SVS structures such as the posterior limitans (PLi) nucleus [156]. The rostral PLi adjacent to the LHb is now termed the PHb and receives M1 ipRGC input [148, 158, 159]. The PHb and nearby thalamic nuclei project to the frontal cortex and nucleus accumbens [159, 160]. Abnormal lighting such as short LD cycles and light at night dysregulates mood via the PHb in addition to disturbing the SCN and clock functions [159, 161–164]. The LHb, which controls the midbrain dopamine and serotonin neurons, is critically involved in mood regulation [165]. In addition, it may function in photosomnolence. Despite sparse retinal input, the LHb receives inputs from the retinorecipient IGL/VLG and SCN and is light-responsive [53, 158, 166–169]. Its activation by light at night may inhibit the VTA dopamine neurons to promote sleep. Light may also facilitate sleep by activating the SCN, which inhibits the VTA via relay through the medial preoptic nucleus [170]. Interestingly, *Sox14*$^+$ neurons in the IGL/VLG receive light input from the M4 ipRGCs and inhibit the LHb [157, 165]. Daytime bright light may activate this pathway to stimulate the VTA dopamine neurons and reduce excessive sleep in a mouse model of depression [165, 171]. Daytime bright light can also benefit health via boosting circadian amplitude [14, 137].

The superior colliculus (SC) of the SVS also regulates midbrain dopamine neurons and is implicated in sleep control [172–174]. Its superficial layers receive heavy innervation by conventional RGCs and weak ipRGC input [153]. GABAergic neurons therein are activated by light and inhibited by darkness, and they exert direct inhibition over dopamine neurons of the VTA [130]. Their ablation in mice prevents the induction of wakefulness by darkness, but without effect on sleep induction by light [130]. RGCs also innervate glutamatergic neurons in the superficial layers of SC, and glutamatergic neurons in the intermediate and deep SC layers are the major source of tectonigral projection [175, 176]. The roles of SC glutamatergic neurons in photosomnolence remain to be determined.

Neural mechanism for the positive masking effects of light on alertness and locomotor activity in diurnal animals

In contrast to its photosomnolence effect in nocturnal animals, bright light increases alertness in humans and general activity in diurnal rodents [146, 177]. Worthy of note here, the wheel-running assay is reliable to reveal light's masking effects in nocturnal rodents, but may yield conflicting results in diurnal animals. For example, one study showed that light inhibits wheel-running but promotes general activity in the Nile grass rats, while others found that light inhibits wheel-running in night-active grass rats and degus but may promote it in day-active ones [92, 178, 179]. Such results raise issues about the nature of wheel-running and its regulation by light. Below we discuss the direct effects of light on diurnal animals' behaviors other than wheel-running.

The direct effects of light in diurnal animals are most comprehensively characterized in the Nile grass rats [100]. Consistent with the sophistication of cone vision in diurnal animals, retinal cone number and sizes of the optic tract, LGN, and SC are increased in the Nile grass rats relative to nocturnal rodents [180, 181]. Overall, light promotes general activity in this species [177]. However, such effect is dramatically altered after lesioning components of the SVS. IGL lesion reverses the masking response, such that light inhibits locomotor activity in the Nile grass rats [182]. Moreover, the lesioned grass rats become night-active [182]. Lesioning the olivary pretectal nucleus (controlling VLG activation by light as well as the PLR) impairs VLG activation and reverses the masking response, although grass rats remain day-active after the lesion [183]. SC lesion suppresses grass rats' activity during the light phase of the LD cycle without changing their chronotype [184]. In contrast to SVS lesions, LSPZ and/or SCN lesion in the grass rats does not impair positive masking [185]. Brain areas mediating the negative masking effect of light, unveiled after SVS lesions, remain to be determined in the Nile grass rats.

Why and how the overt effects of light on behavior diametrically differ in nocturnal and diurnal animals? An interesting possibility lies in altered retina signaling to brain , which is exemplified by the *Rpe65*$^{-/-}$*;Opn4*$^{-/-}$ mutant mice [99]. In contrast to the nocturnal WT mice, those mutants are entrained to the LD cycle but active during the light phase – they become diurnal [186]. This phenomenon, termed diurnal entrainment, is not due to positive masking, since darkness suppresses wheel-running in the mutants [186]. Instead, it was argued that ipRGCs of the mutant mice primarily signal OFF responses, such that light is perceived as darkness by the brain, accounting for the chronotype switch [187]. Under normal lighting, ipRGCs of WT animals signal ON responses. However, some ipRGCs (probably enriched for the M1 type in mice) use GABA instead of glutamate as the neurotransmitter [188]. Their activation by light can mimic the OFF response in effect. While stimulating the RHT mainly evokes excitatory responses in the SCN of nocturnal animals, a much higher proportion of inhibitory responses is seen in diurnal animals, suggesting increased GABAergic M1 ipRGC input therein [136]. This could reduce SCN's sensitivity to the entraining and masking effects of light in diurnal animals. Meanwhile, increased GABAergic M1 input to the IGL/VLG may weaken ENK neurons' activation by light, while non-M1 RGC input to NPY neurons is probably increased due to enhanced pattern vision. The balance between the opposing effects of light on behavior would be tipped toward positive masking in diurnal animals.

Summary and perspective

Light entrains the SCN clock to regulate circadian rhythms. Besides this indirect route, light also acts on the SCN and extra-SCN structures to exert direct influences on mammalian physiology and behavior. Both the direct and indirect effects of light are of fundamental importance to temporal niche specialization. While research over the past 20 years enables in-depth understanding of the direct effects of light via the the ipRGCs, technical advances in the future might allow improved knowledge about the brain targets and functions of diffrent ipRGC types in model animals such as mice and even diurnal species including primates. The roles of distinct neuron types in SVS structures such as the IGL/VLG in mediating light's opposing effects on behavior should also be characterized in more detail in both diurnal and nocturnal species.

The effects of light on circadian rhythms and health depend on circadian time, and the circadian visual system and classical visual system mostly differ in their sensitivities to light intensity and spectrum. Taking those knowledges into account is essential for the effective use of light therapy to treat human illness and appropriate lighting design and practice to benefit health [17, 189]. For example, daytime bright light can increase circadian amplitude and improve mood and cognition in animals and humans, whereas light at night potentially disturb circadian timing and should be limited whenever possible. Adjusting light intensity and spectrum according to the time of day to maintain circadian homeostasis would be a good practice in both professional and personal lives [189].

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