NEURAL CIRCUITS

Illuminating a path from light to depression

Our light environment can strongly influence our mental health. Kai An and colleagues dissect the neuronal circuit mediating depression-related behaviors induced by mistimed light input in mice, implicating the nucleus accumbens as the downstream target of the neural pathway between intrinsically photosensitive retinal ganglion cells and the perihabenular nucleus.

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From the lights in our homes to the glowing phone screen as we read that one last tweet before bed, light at night is firmly embedded in our daily lives. We are conscious of the convenience light provides in allowing us to see and continue our tasks long after sunset. What we fail to appreciate is the profound and often subconscious effect this light input has on our physiology and behavior, which can range from disruptions in hormone levels to changes in mood and cognitive function. In this issue of *Nature Neuroscience*, An et al. investigate the circuit mechanism underlying the detrimental effect of light at night on mood, focusing on the perihabenular nucleus (pHb) and its two of its main output targets[1]. Light is a powerful stimulus that influences a range of complex behaviors and physiological functions. Consequently, mistimed light information can have significant negative impacts on health. This is observed in the consequences of shiftwork, seasonal changes in day length, shifts from standard to daylight savings time and trans-meridian travel, which all result, to varying degrees, in changes in mood and cognitive function and increased risk for the development of psychiatric disorders[2–5]. The effect of light on mental health under these circumstances has long been thought to occur through its influence on circadian rhythms and sleep. While a substantial body of evidence supports the existence of these indirect mechanisms, a more direct role for light in regulating behaviors related to mental health has emerged[6].

Studies in humans and animal models have demonstrated the ability of light to influence mood-related behaviors and activity of the brain regions that regulate such behaviors[7–9]. Initial work investigating this direct effect of light identified a specialized subset of retinal ganglion cells that are intrinsically photosensitive (ipRGCs) as the conduit for conveying this non-visual light information from the eye to the brain[10]. Most retinal ganglion cells convey visual light information from photoreceptors (rods and cones) to brain regions that support image formation. In addition to receiving rod/cone input, ipRGCs are able to directly transduce light information[11,12], and they project throughout the brain to convey light information to regulate a variety of physiological functions[13]. A recent study by Fernandez et al. identified the pHb as the ipRGC target mediating the light-dependent effects on mood regulation[9]. They determined that the pHb receives input from ipRGCs and projects to the medial prefrontal cortex (mPFC) and nucleus accumbens (NAc), thus serving as a relay for light information to two brain regions regulating depression-related behaviors.

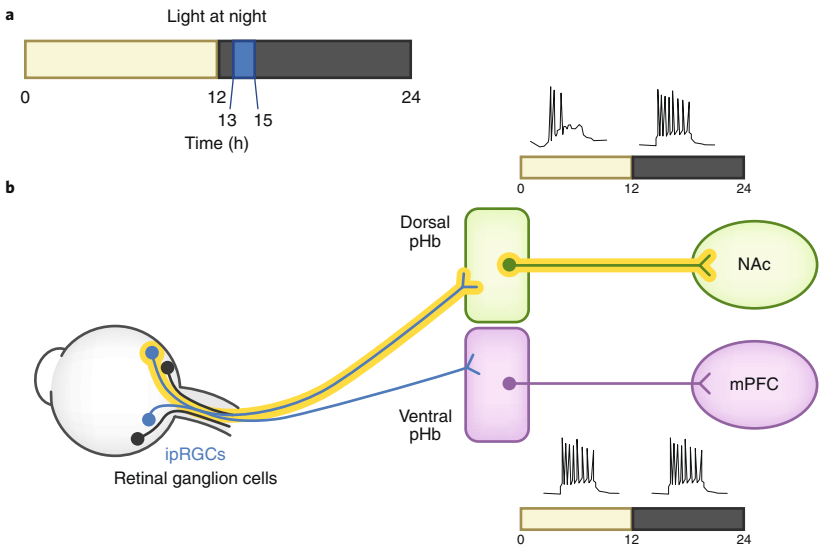

Fig. 1 | Neuronal circuits underlying effects of light at night on mood. a, The LAN paradigm used to induce depression-related behaviors in mice. Mice are housed in 12 h of light (yellow) and 12 h of darkness (black), with a 2-h blue light pulse beginning 1 h after lights-off. **b**, Schematic of proposed model. Nighttime light information is conveyed by ipRGCs to the pHb. Dorsal pHb neurons, which show increased excitability and light sensitivity at night, convey nighttime light information to the NAc to mediate LAN-induced depression-related behaviors. Ventral pHb neurons, which target the PFC, do not show the same time-of-day-dependent modulation and are not required for the effects of LAN.

In this issue, An et al. expand upon this seminal work, providing deeper insight into the consequences of light at night and the physiology of the pHb, highlighting the ipRGC–pHb–NAc circuit in regulating light-dependent effects on mood related behaviors[1].

To model the effects of light at night (LAN) on brain circuitry, Kai An and colleagues use a light cycle in which mice are exposed to 12 h of light and 12 h of darkness with a 2-h blue light pulse beginning 1 h after the onset of darkness (Fig. 1a). Mice exposed to this light–dark cycle for 3 weeks have normal circadian rhythmicity, but show an increase in depression-related behaviors, including decreased sucrose preference and increased immobility in the forced swim

test, considered to be behaviors modelling anhedonia and helplessness, respectively. This light-dependent effect is similar to that initially observed in response to the T7 light cycle (3.5 h light, 3.5 h dark)[10]. Whereas the T7 cycle exposes mice to light at all different circadian times, the LAN paradigm presents light at the same circadian time each day, allowing the authors to specifically test the effects of light at night. Using various retinal mutants, optogenetics and lesioning, An et al. show that ipRGC innervation of the pHb is required for the effects of LAN on depression-related behaviors[1], furthering the conclusions from Fernandez et al. that the ipRGC–pHb circuit serves as a critical mediator for the effects of light on mood regulation.

Fernandez and colleagues mapped pHb projections to the mPFC and NAc, identifying these areas as potential targets for light-dependent regulation of mood[9]. Using dual-color neuronal tracing, An et al. expand upon this to map two distinct, non-overlapping populations of pHb neurons organized anatomically, with NAc-projecting neurons located in the dorsal pHb and mPFC-projecting neurons in the ventral pHb. These two populations of pHb neurons appear to differ in terms of electrophysiological properties and light sensitivity. Dorsal pHb neurons exhibited robust time-of-day-dependent changes in intrinsic excitability, with increased excitability at night; similarly, these neurons show increased light responses at night as measured by in vivo fiber photometry. In contrast, ventral pHb neurons do not show time-of-day-dependent modulation of these properties and are less robustly sensitivity to light. Taken together, these data define discrete neuronal pathways that can be distinguished anatomically and electrophysiologically (Fig. 1b). The time-of-day-dependent modulation observed in dorsal pHb neurons suggests a potential role for gating by the circadian system, rendering the dorsal pHb–NAc pathway more sensitive to mistimed light input.

In support of this idea, the authors find that pHb–NAc, but not pHb–mPFC, input is required for LAN-induced depression-related behavior using a conditional virus approach to target and specifically silence each pathway. Accordingly, acute activation of the pHb–NAc pathway, but not the pHb–mPFC pathway, was sufficient to induce avoidance behavior as measured by real-time place avoidance and depression-like behavior as measured by a decrease in sucrose preference, but the authors observed no change in behavior in the forced swim test. However, chronic activation of pHb–NAc was sufficient to induce depression-related behaviors in both tests. This difference between these results may serve to highlight inherent complexities of the different behaviors being tested and partially overlapping neuronal circuit function.

The NAc and mPFC are distinct targets of the pHb, but are also interconnected with one another[14]. The work from An et al. raises interesting questions regarding the functional connectivity of these regions and the integration of light information in modulating these circuits. Perhaps the NAc is more sensitive to acute light information as a means to modulate reward-seeking behavior in response to immediate, salient environmental stimuli. For example, someone sneaking around in a dark kitchen might abandon their quest for a midnight snack when someone else turns on the kitchen light, and the shift in the perceived value of this reward is reflected in subsequent NAc activity as a result of a sudden change in pHb–NAc input. Chronic light information, on the other hand, may have longer lasting and/or more-widespread effects on the brain, engaging changes in both the NAc and mPFC to influence behavior. An et al. did not test chronic activation of the pHb–mPFC pathway, but Fernandez et al. found that chronic activation of this pathway increased depression-related behaviors in the forced swim test and tail suspension test[9]. Together, these studies raise the possibility that mistimed light input engages disparate brain regions subserving a variety of behaviors and may do so differently across different timescales. This would result in multiple changes in those various behaviors, paralleling the myriad of behavioral symptoms observed in the multifaceted disorder of human depression. One might even speculate that mistimed light input engages these different pathways differentially based on an individual's unique biological risk profile, inviting further study as we consider the translational implications of these fascinating findings.

The results from An and colleagues further our understanding of how our light environment can influence our mental health and the neuronal pathways involved in that process. Future work measuring neuronal activity in awake, behaving mice will determine how the light environment influences neuronal activity in these regions and will dissect differences between acute and chronic light exposures. This will be critical for understanding the detrimental effect of mis-timed light on brain function and mental health. Additionally, this area of study will be crucial for understanding the mechanisms underlying the beneficial effect of properly timed light, as light therapy has been demonstrated to be an effective treatment for depression (most notably in seasonal affective disorder) as well as neurological disorders including delirium and dementia[15,16]. It should also inform development of optimally timed light paradigms for humans in extreme light–dark environments like space and high latitudes or for people performing night or shift work.

The work described here illuminates the challenges our increasingly global and 24-h society faces in balancing mental health against the convenience and productivity gains of being 'always on', but also lays the groundwork for how these findings might be expanded to cognition and mental health maintenance and, eventually, targeted therapeutic intervention.

Now, after you read the rest of this issue, put away this glowing screen until daytime. ❐

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Competing interests

The authors declare no competing interests.