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THEORETICAL REVIEW

Non-circadian direct effects of light on sleep and alertness: Lessons from transgenic mouse models

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SUMMARY

Light exerts a strong non-visual influence on human physiology and behavior. Additionally light is known to affect sleep indirectly through the phase shifting of circadian rhythms, and directly, promoting alertness in humans and sleep in nocturnal species. Little attention has been paid to the direct non-image-forming influence of light until recently with the discovery and emerging knowledge on melanopsin, a photopigment which is maximally sensitive to the blue spectrum of light and expressed in a subset of intrinsically photosensitive retinal ganglion cells. Indeed, the development of transgenic mouse models targeting different phototransduction pathways has allowed researchers to decipher the mechanisms by which mammals adapt sleep to their light environment. This review summarizes the novel concepts and discrepancies from recent publications relating to the non-circadian effects of light on sleep and waking. Specifically, we discuss whether darkness, in addition to light, affects their quality. Furthermore, we seek to understand whether longer sustained periods of light exposure can influence sleep, if the direct photic regulation depends on time of day, and whether this affects the homeostatic sleep process. Moreover, the neural pathways by which light exerts a direct influence on sleep will be discussed including the respective role of rods/cones and melanopsin. Finally, we suggest that light weighs on the components of the flip-flop switch model to induce respectively sleep or waking, in nocturnal and diurnal animals. Taking these data into account we therefore propose a novel model of sleep regulation based on three processes; the direct photic regulation interacting with the circadian and homeostatic drives to determine the timing and quality of sleep and waking. An outlook of promising clinical and non-clinical applications of these findings will be considered as well as directions for future animal and human research.

Introduction

Exposed to the terrestrial light–dark cycle and required to adapt to permanent changes in ambient light, all human beings experience the powerful influence of light. Since the emergence of our self-awareness, the relationship between mankind and light has always been prevalent, and the sun, our principal source, has become a major component of our shared cultural history. In numerous societies the deification of the sun is evident: from the Mayan pyramids of Mesoamerica, to the cathedrals of medieval Europe, deliberately constructed to bathe their worshipers in light. In fact, religious iconography often involves reference to the divinity of light. It has become a symbol of knowledge, the root of the word "enlightenment", and a way of describing intelligence (bright). In its absence we believe we are lost; sightless from awareness and development. Light thus simultaneously serves as our agent of progress and our continued emancipation as a species.

Light affects a broad range of physiological parameters and behavior,[1] including sleep and alertness,[2] mood,[3,4] and cognition,[5,6] both indirectly, through the phase shifting of circadian rhythms, and directly, in a circadian independent fashion. Therefore, in addition to aligning sleep and waking with time of day, light also acutely promotes alertness in humans, and sleep in nocturnal species.[7–9] Whereas the indirect influence through the entrainment of the circadian timekeeping system to the ambient light–dark cycle was the main focus for the last several decades, the direct effects of light have received little attention from chronobiologists, who commonly referred to it as a "masking effect",[10,11] shrouding it in the evaluation of circadian rhythms.

Light enters the organism through the eyes and characterization over the last two decades of the pathways by which photic

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Abbreviations

5-HT	serotonin
ADTA	ablated diphtheria toxin-A
ANOVA	analysis of variance
CNGA3	cyclic nucleotide-gated channel alpha 3
EEG	electroencephalogram
fMRI	functional magnetic resonance imaging
GNAT1	guanine nucleotide-binding protein subunit alpha-1
IGL	intergeniculate leaflet
ipRGCs	intrinsically photosensitive retinal ganglion cells
KO	knockout
LD	light–dark
LH	lateral hypothalamus
NREM	non-rapid eye movement
OPN	olivary pretectal nucleus
Opn4	melanopsin photopigment
Opn4	opsin-4 (melanopsin)
OPT	olivary pretectum
PER3	period circadian protein homolog 3
PET	positron emission tomography
rd/rd cl	rodless/coneless
REM	rapid eye movement
RGC	retinal ganglion cell
SC	superior colliculus
SCN	suprachiasmatic nuclei
SPVZ	subparaventricular zone
VLPO	ventrolateral preoptic nucleus
WT	wild type
ZT	zeitgeiber time

information is conveyed to the brain was crucial for understanding its non-visual effects. Rods and cones are essential for animals to generate an image of the world, yet vision is not their only function. They also provide a measurement of light irradiance and contribute to non-visual functions such as photoentrainment and pupillary constriction.[12,13] As early as 1984, Takahashi and colleagues noted the presence of an unusual spectral sensitivity in the photoreceptive cells of hamsters, which affected circadian rhythms and seemed separate from the visual system.[14] The first evidence of a non-visual light system impacting physiology in humans was shown in blind patients wherein suppression of melatonin was seen following exposure to light,[15] later confirmed by others.[16–18] This observation that photoentrainment persists in the absence of rods and cones, was further demonstrated in animals and served as a critical step toward the discovery of a third component, melanopsin.[19,20] Melanopsin (Opn4)[21] is a photopigment crucial for irradiance detection and particularly sensitive to the blue spectrum of light (peak at 460–480 nm). This protein is expressed in a subset (1–2%) of retinal ganglion cells termed intrinsically photosensitive (ipRGCs), and is tightly linked to the non-visual functions of light.[22–24] These ipRGCs integrate the irradiance signal from both rods and cones and melanopsin-based pathways, transferring light information to various areas of the brain and representing the essential conduit for non-visual functions.[25,26] However, as previously stated most characterization of the non-visual functions of light has focused on output, such as circadian entrainment or constriction of the pupil.[12,13] In humans the direct (non-circadian non-image-forming, referred to subsequently as "direct") effects of light when administered at night, especially short wavelengths, have been shown to affect vigilance, attention, and waking electroencephalogram (EEG),[27] suggesting that the visual photopic system is not the primary photoreceptor system mediating these responses to light. Until recently, little was known about the significance of photoreceptors in regard to their mediation of the direct effects of light on sleep, in part because these photic inputs were difficult to distinguish from the influencing effects of the visual or circadian processes. Over the last few years, the discovery of melanopsin and subsequent development of transgenic models targeting the phototransduction pathways has allowed researchers to revisit the effects of light on behavior. Several groups[28–30] recently demonstrated that alteration of the light input to the brain by genetic ablation or inhibition of phototransduction components (rods and cones, Opn4, or ipRGCs) severely affects both sleep and waking. These data not only reveal a deeper and more complex role of light than was previously thought, but raise critical questions on how the direct effects of light interact with the circadian and homeostatic processes to determine the timing and quality of sleep and waking.

The mirrored effects of light and darkness are mediated through melanopsin and rod/cone-based phototransduction: a proof of concept

In order to quantify the acute sleep photic regulation and to determine the respective contribution of rods/cones and melanopsin-based pathways, three teams independently analyzed sleep in response to a light or dark pulse using different transgenic mouse models. To compare the results between studies, we normalized the data by setting the sleep response to a light pulse at 100% for the respective controls (wild type; WT) of each of the different transgenic mouse models, and by analyzing the same duration of pulse (only the first hour; Fig. 1). This assessment is appropriate given the comparable parameters of the light pulses used by each of the groups. All three studies used similar lighting

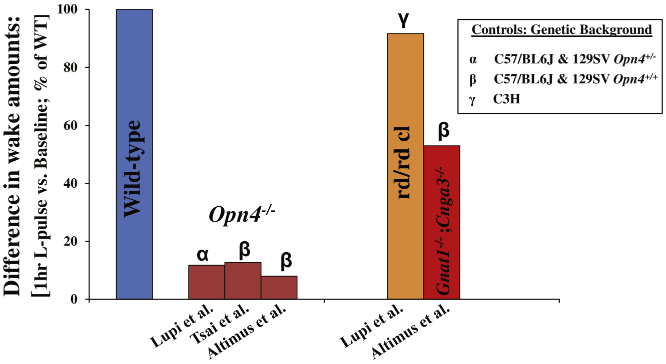

Fig. 1. Differences between studies in wake amounts during a 1-h light pulse administered at the same zeitgeiber time (ZT) (early part of the dark phase). Effect of a 1-h light pulse administered at ZT14, ZT15, or ZT16 on wake suppression in different transgenic mouse models (maintained under 12-h:12-h light–dark cycle; 12 hL:12 hD). The data were extrapolated from different studies[28–30] and expressed as a deviation from their respective controls (symbols, α, β, γ, indicate the genetic background used in each of the studies) that are normalized to 100%. No s.e.m. is given nor statistics done due to the availability of the data extrapolated. *Opn4*$^{+/+}$ represents the wild-type (WT) control against *Opn4*$^{-/-}$, however Lupi et al. used heterozygous *Opn4*$^{+/-}$ animals as controls. *Opn4*$^{-/-}$ melanopsin knockout; rd/rd cl: rodless coneless; *Gnat1*$^{-/-}$; *Cnga3*$^{-/-}$: mutations in the rod transducin gene (*Gnat1*) and the cone cyclic nucleotide-gated channel gene (*Cnga3*) resulting in intact melanopsin-based photoreception but lack of ability of both rods and cones to detect light.[12] Wake was chosen as the output measure as Altimus et al. categorized sleep as a whole and did not distinguish between NREM and REM sleep, and though a 3-h light pulse was given during this experiment, only data from the first hour were used so as to compare with the other two studies. Percentages for Altimus have been converted into minutes/hours.