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PHYSIOLOGICAL REVIEW

Alerting effects of light ☆

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Non-image forming visual system;
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Thermoregulation

Summary Light exerts powerful non-visual effects on a wide range of biological functions and behavior. In humans, light is intuitively linked with an alert or wakeful state. Compared to the effects of light on human circadian rhythms, little attention has been paid to its acute alerting action. Here I summarize studies from the past two decades, which have defined and quantified the dose (illuminance levels), exposure duration, timing and wavelength of light needed to evoke alerting responses in humans, as well as their temporal relationship to light-induced changes in endocrinological and electrophysiological sequelae of alertness. Furthermore, neuroanatomical and neurophysiological findings from animal studies elucidating a potential role of light in the regulation of sleep/wake states are discussed. A brief outlook of promising clinical and non-clinical applications of lights' alerting properties will be given, and its involvement in the design of more effective lighting at home and in the workplace will be considered.

Introduction

The definition of light in current encyclopedias is predominantly limited to its physical explanation as the visible part of the electromagnetic spectrum. However, precisely speaking, our eyes cannot see a spectrum, it is rather the photoreceptors, i.e., rods and cones in the eyes which collect, decipher and transpose the emission or reflectance of electromagnetic waves in a specific range or photons into meaningful visual signals in our brain. However, light serves for much more than just vision in humans. Sunlight acts via the skin for the synthesis of vitamin D or to reduce serum bilirubin in neonatal jaundice. Some totally blind people even show physiological responses to light stimuli without consciously seeing them. Seen in a historical context, *light* in old Egypt had such a central role that Egyptian theology under the reign of Akhenaten has been designated as the "theology of light" by Egyptologists.[1] As a consequence, night and darkness were negatively characterized as times without sunlight during which humans and animals remain in their homes as dead until the sun rises again. According to Akhenaten, light makes life possible while darkness symbolizes death. It was maybe also the "theological aspect" of light in the following millennia which precluded its scientific investigation in humans.

☆ Dedicated to Anna Wirz-Justice in recognition of her contributions to the field made during her career at the Psychiatric University Clinics Basel.

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It is only two decades since the entraining and phase-shifting capacity of light on human circadian rhythms was discovered. It has been the primary research focus since. Relatively little attention has been paid to other effects of light on the human brain, such as its alerting properties. As of 1995, only a handful of studies had directly or indirectly examined the immediate activating effects of light on alertness, performance and/or mood.[2,3] This has recently changed since Berson et al.[4] detected a novel, third type of photoreceptor in the retina of mammals. This novel photoreceptor cell type, an intrinsic photosensitive retinal ganglion cell, is considered to play a crucial role in many of the non-visual biological effects of light also in humans. The existence of such a photoreceptor can explain why pupil constriction, melatonin suppression and circadian entrainment are still possible in rodless–coneless transgenic mice.[5,6] Similarly, studies in humans have indicated that partial or complete loss of the visual system still allows for normal melatonin suppression and circadian phase shifting.[7,8] Recent studies have shown that transfecting non-photosensitive cells with the melanopsin gene confers light sensitivity to these cells, which provides compelling evidence for melanopsin being the functional photopigment of the photosensitive retinal ganglion cells.[9–11] Phylogenetically, melanopsin resembles invertebrate opsins more closely than it does other mammalian opsins (e.g., rhodopsin, cone opsins), indicating that it may have evolved before the vertebrates.[12] Studies of melanopsin-knockout mice, however, demonstrate that although melanopsin plays an integral role in circadian phototransduction, it is not essential for non-visual ocular-mediated responses.[13–15]

The photosensitive ganglion cells have their own neural connections to the suprachiasmatic nuclei (SCN), the site of the principal mammalian pacemaker.[16] Moreover, they also have direct and indirect (via the SCN) projections to brain areas implicated in the regulation of arousal.[16] The spectral sensitivity of melanopsin ganglion cells is different from that of the classical photoreceptors.[12,17] This allows designing human study protocols in which the non-visual effects of light at specific wavelengths (i.e., monochromatic light) can be tested and deriving conclusions about a possible involvement of the new photoreceptors in the alerting response to light.

In the following review, studies on human alerting responses to light and their sequelae (e.g., melatonin, cortisol, core body temperature (CBT), circadian gene expression) will be summarized and discussed within the framework of current concepts of neuroanatomical and neurophysiological findings from animal studies and neural circuitries involved in the regulation of sleep/wake states. A brief outlook of possible clinical and non-clinical applications of lights' alerting properties will be given, with considering its involvement in the design of more effective lighting at home and in the workplace.

Measures of alertness

In healthy people, alertness or sleepiness can be reliably measured by simply asking them or by subjective rating scales. The precise meaning of the terms sleepiness, alertness, fatigue or tiredness may differ between languages and situations (e.g., real life on shift work or constant routine conditions in a sleep laboratory). In general, in the studies on alerting effects of light, standardized fatigue or sleepiness scales have been used, which allow for a good comparison between experiments. The disadvantage of subjective alertness ratings in light studies, however, is that a sighted person is never ''blind'' to the light treatment. He or she may intuitively feel more alert in a more lit environment compared to darkness. There is no real placebo control to light. Thus, more objective measures of alertness are crucial in light experiments, one of them being the psychomotor vigilance test (PVT, a simple reaction time task[18]). The advantage of the PVT is its abundant use in the field of sleep and chronobiology research and its easy ''low-tech'' application. The disadvantage of the PVT is that it measures sustained attention rather than alertness or fatigue *per se*.

Reliable neurophysiological correlates of human alertness comprise electroencephalographic (EEG) frontal low-activity (1–7 Hz) and electrooculographic (EOG) slow rolling eye movements and eye blink rate.[19] The advantage of these measures is their high temporal resolution, which allows detecting micro-sleeps or performance lapses in the range of seconds. A major disadvantage in their use in real life settings (e.g., night shift work conditions in the field) is their interference-prone nature, particularly for the EEG. With functional magnetic resonance (fMRI) and positron emission tomography (PET) techniques one can virtually ''spotlight'' the brain and characterize the neural correlates of the alerting effects of light. The use of fMRI and PET in field studies is unreasonable. Moreover, it is not easy to design a high quality fMRI light protocol.

All of the above-mentioned measures and techniques have been used in the studies cited in the following sections.

Circadian rhythmicity of alertness

From early on, alertness has been related to time of day. Kleitman already noticed that the diurnal modulation of alertness shows a close temporal association with the circadian rhythm of core body temperature with its maximum in the evening and nadir in the early morning.[20] More recently, the contribution of circadian rhythmicity to alterations in subjective alertness has been quantified in forced desynchrony protocols.[21–23] These protocols revealed that the contribution of the circadian pacemaker to variations of subjective alertness, performance and sleep propensity was equal to the contribution of the sleep homeostat. The data further revealed that the detrimental effects of prior wakefulness on alertness were strongest close to the minimum of the endogenous core body temperature rhythm. The interpretation of these data led to the conclusion that stable and high levels of alertness can only be maintained when the phase relationship between the endogenous circadian timing system and the sleep/wake cycle is such that the circadian timing system opposes the wake-dependent deterioration of alertness and performance as conceptualized in the ''opponent process'' model.[24] This is achieved most effectively when the waking day is initiated approximately 2 h after the endogenous circadian minimum of the core body temperature rhythm, which corresponds to approximately 3 h after the circadian maximum of the plasma melatonin rhythm. Thus, at least in humans, it seems that the circadian process represents a wake-promoting drive to balance the accumulating homeostatic drive for sleep during wakefulness (for a review see Ref. [25]).

To allow for sleep inertia, a transitional state of lowered arousal experienced upon awaking from sleep, and additional process, process W, was introduced besides the circadian and the sleep homeostatic process.[26] Sleep inertia has been shown to exert a detrimental effect on cognition that last up to 4 h after awakening, depending on prior sleep duration.[27] Thus, it is closely related to the circadian and homeostatic process and should not be underestimated in its repercussion on alertness.

Considering the temporal dynamics of the impact of these three processes on alertness, one could postulate that light should exert its alerting action most strongly when the circadian drive for sleep is at its maximum (i.e., in the early morning at the CBT minimum), under high homeostatic sleep pressure (i.e., after more than 16 h of wakefulness) and during sleep inertia (i.e., upon awaking from sleep).

Timing

Most studies on the alerting properties of light have been conducted during the nighttime hours (e.g., during simulated night shift work in the laboratory or under field conditions). This makes sense from a circadian perspective since the circadian drive for sleep is maximal during the night between 2 and 6 a.m., and the homeostatic drive for sleep usually rises when exceeding 16 h of prior wakefulness (i.e., elevated sleep pressure). Although different light intensities and light exposure durations have been used, the nighttime studies unequivocally showed alerting properties of light if compared with a dim light condition.[28–36] Most of these studies have concluded that this effect is an indirect consequence of the capacity of light to suppress melatonin, since correlational data have generally (but not always[34]) supported this conclusion (Figure 1). A variety of studies have provided evidence that melatonin suppression may be involved in both the subjective alerting effect as well as the effect of light on EEG activity during wakefulness.[30,32,37] Administration of supraphysiologic doses of melatonin (e.g., 5 mg) led to an increase in sleepiness and changes in the waking EEG opposite to those induced by bright light, and the effect of light on the EEG and sleepiness could be counteracted by exogenous melatonin.[32] It has been hypothesized that melatonin elicits these effects by attenuating SCN-dependent mechanisms responsible for promoting and maintaining cortical and behavioral arousal at particular times in the circadian cycle.[38–40] Although melatonin suppression mediated by the retinal projection to the SCN is likely to be involved in some of the direct effects of light at night, other possibilities should also be considered, particularly since recent work,[34,41,42] in contrast to previous reports,[35,43] shows that light exposure can enhance alertness even during daytime hours, when circulating melatonin levels are virtually undetectable (Figure 2). Furthermore, PET results on the effects of polychromatic light exposure during the biological night indicated that alerting responses are not only confined to hypothalamic areas in the vicinity of the SCN but extend to modulation of a large-scale network of cortical areas involved in attention, particularly a large-scale occipito-parietal attention network, including the right intraparietal sulcus.[44] Similarly, a short exposure to bright light during daytime could transiently prevent the sleepiness developed in continuous darkness in a recent fMRI study.[42] The light-induced increase in subjective alertness corresponded with enhanced responses in the posterior thalamus, including the pulvinar nucleus,[42]

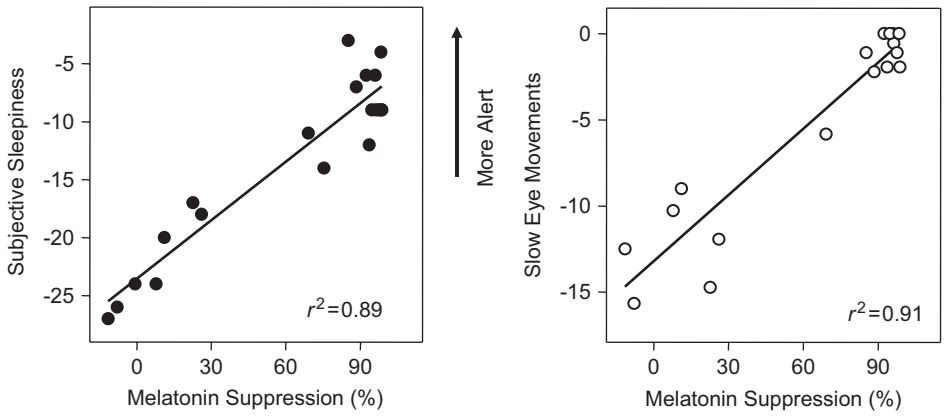

Figure 1 Positive correlation between lights' alerting response and plasma melatonin suppression for subjective alertness and the incidence of slow eye movements. Data from Cajochen et al.[30] and Zeitzer et al.[31]

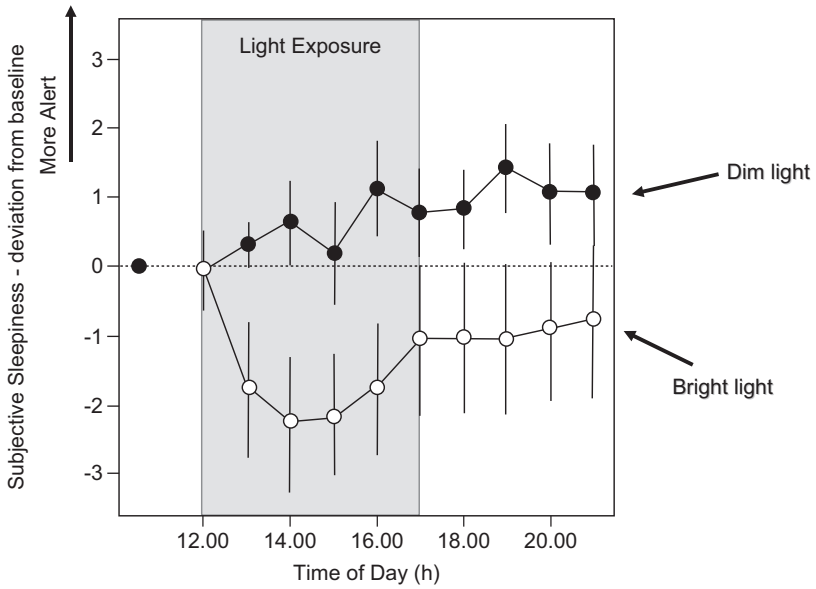

Figure 2 Mean ($\pm$SE) deviations from baseline of subjective sleepiness for the bright light group (○) ($N = 7$), exposed to approximately 1000 lx between noon and 5:00 p.m., and the dim light group (●) ($N = 8$), exposed to less than 5 lx throughout the same time period. The shaded area represents the period of bright light exposure. The dashed horizontal line represents the baseline, as determined from individual mean sleepiness scores from 9:00, 10:00, and 11:00 a.m. Negative deviations represent decreases in sleepiness relative to baseline. Positive deviations represent increases in sleepiness relative to baseline. Redrawn from Phipps-Nelson et al.[46]

which has been implicated in visual pattern discrimination, visual attention and alertness regulation.[45] Light exposure also induced an increase of activity in a large scale cortical network, involving parietal, temporal, occipital and insular areas involved in the attention task subjects were performing.[42] Unfortunately, the results of the nighttime[44] and the daytime[42] exposure imaging studies can not be compared directly, since PET and fMRI methods require different experimental designs, and their spatial and temporal resolution differ considerably. Thus, it will be interesting to conduct a fMRI study specifically investigating time of day effects of the alerting impact of light and the neural circuits involved.

In summary, there are only very few studies comparing daytime vs. night time alerting effects of light, and all of them used bright polychromatic light ($\geqslant$1000 lx). This is a sufficient intensity to elicit maximal alerting effects (see below) and thus may not show time-dependency. Before one concludes that the alerting action of light is independent of time of day, a phase response curve to lights' alerting effects needs to be determined ideally with light intensities of typical room light (90–180 lx) in non-sleep deprived subjects.

Dose

In early studies looking at the alerting properties of light, relatively high irradiances (i.e., 1000 lx or more) of white polychromatic light were used.[31,35,36,46–50] This was because the first demonstration of a physiological effect of light was Lewy's discovery in 1980 that at least 1000 lx of white light was required to suppress melatonin in healthy humans.[51] This finding led to the assumption that, in contrast to animals, humans require much higher light irradiances to suppress melatonin. Under normal circumstances, ordinary room light intensities (100–200 lx) would not suppress melatonin levels.[52] However, Brainard et al.[53] already showed in 1988 that under carefully controlled laboratory conditions and with artificially dilated pupils light irradiances in the range 1.03–5.50 lx can elicit significant melatonin depression in humans.

The question remained whether similar dose–response relationships exist for the alerting properties of light. To answer this question we exposed men and women in a carefully controlled dose response protocol to illuminances ranging from 3 to 9100 lx of white light for 6.5 h during the early biological night after they had been exposed to <3 lx for several hours.[54] Light exerted an acute alerting response as assessed by a reduction in the incidence of slow-eye movements, a reduction of EEG activity in the theta-alpha frequencies (EEG power density within the 5–9 Hz range) as well as a reduction in self-reported sleepiness. In accordance with the dose response function for human circadian resetting and melatonin suppression,[55] the responses of all three indices of alertness to variations in illuminance were consistent with a logistic dose response curve. Half of the maximum alerting response to bright light of 9100 lx was obtained with room light of $\sim$100 lx (Figure 3). The characteristic of the dose response functions described for the alerting effects of light may imply that these effects are mediated by the same photoreceptive elements and retinohypothalamic pathways that mediate the circadian responses to light. However, the proper approach to investigate this aspect would be a spectral study where alertness changes are measured in response to wavelengths across the entire visible spectrum.

There is considerable evidence that the circadian photoreceptive system is functionally and structurally distinct from the image forming visual system.[16] Key characteristics that distinguish the circadian photoreceptive system include the relatively high threshold for responses to light and the long duration stimulus integration time.[56,57] In addition, it has been suggested that the circadian photoreceptive system does not exhibit adaptation to previous light exposure,[57] although recent human studies indicate that a higher intensity prior light history dampens the magnitude of subsequent melatonin suppression by light by

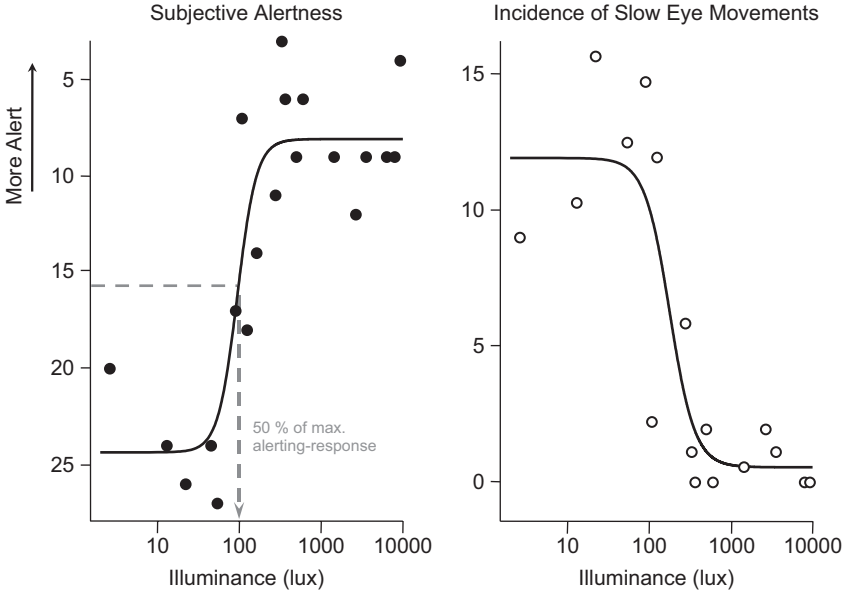

Figure 3 Dose–response relationship between illuminance and subjective alertness, and the incidence of slow eye movements. Data points represent the sum of alertness ratings and the number of 30-s epochs containing at least one slow eye movement during the last 90 min of the light exposure episode for a single individual. The line represents a logistic regression model fit to the individual data points. Modified from Cajochen et al.[30]

about 10–15%.[58,59] The potential role of adaptation of this circadian photoreceptive system is important for the implications of the dose–response curve for lights' alerting effects. If adaptation does not play a major role (10–15% under laboratory conditions), the dose–response relationship for lights' alerting action in the laboratory can be expected to be valid also for real life situations in which subjects may have been exposed to higher light intensities during the day. However, whether less melatonin suppression due to adaptation to previous light exposure also means less of an alerting response needs further investigation. At least our data indicate that variations in illuminance within the range of typical, ambient room light (90–180 lx) can have a significant impact on subjective alertness and its electrophysiologic correlates during the early biological night. This relatively high sensitivity may explain why in some previous experiments a direct alerting effect of light was not observed as the effects of "bright light" were compared to "dim light" conditions that were of sufficient intensity to elicit near-maximal effects.[47,48]

Wavelength

The relationship between the wavelength of light and its alerting response has been investigated in four studies so far.[60–63] All of them reported superiority of short wavelength light (470 nm and lower). We compared a 2-h evening exposure to monochromatic light of two different wavelengths (460 and 550 nm) at very low intensities (photopic range: 5.0 lx for 460 nm and 68.1 lx for 550 nm) in non-pupil dilated subjects.[60] Although the subjects' pupils during the blue (460 nm) light treatment were more constricted than during the green (550 nm) light condition, thus resulting in a geometric reduction of light illuminating the retina, subjects felt more alert during the 460 nm than the 550 nm light (Figure 4). They also had an attenuated evening increase in melatonin along with an attenuated decrease in core body temperature and heart rate only under the 460 nm light compared to 550 nm light and a dark control condition. We also have the first evidence that induction of circadian gene PER2 expression is selectively stimulated by exposing subjects to 2 h

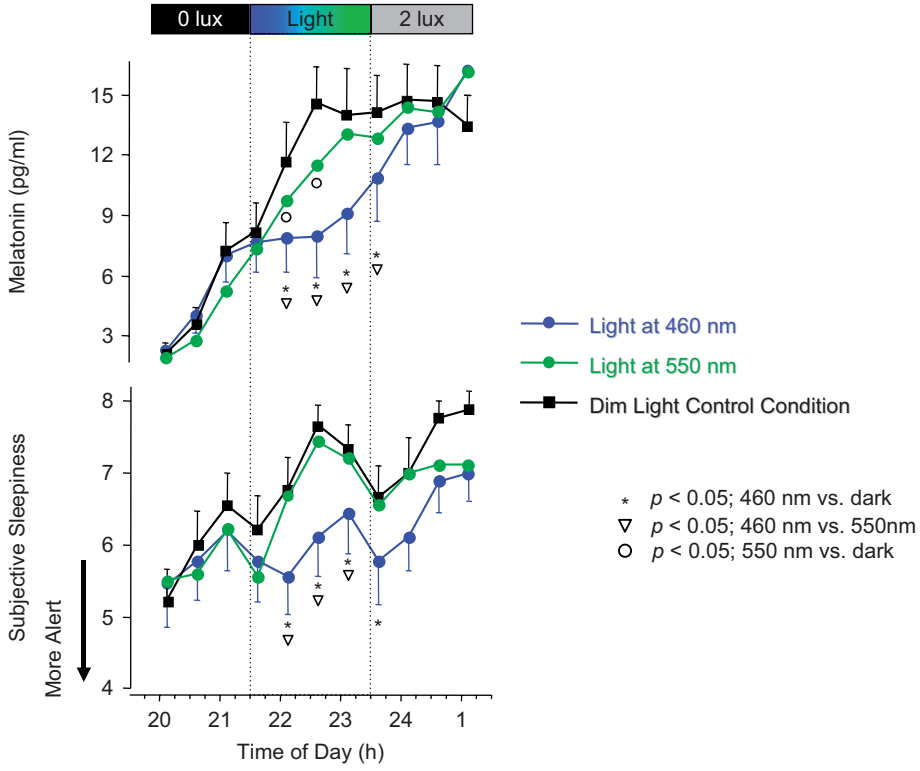

Figure 4 Effects of a 2-h light exposure at 460 nm (●), 550 nm (●), and no light (■) in the evening under constant posture conditions (i.e., supine in bed) on salivary melatonin levels and subjective sleepiness [mean values ($n = 9$) and SEM]. For clarity, the SEM values for the 550-nm light condition were not plotted. Significant *post hoc* comparisons ($P < 0.05$; Duncan's multiple range test corrected for multiple comparisons) are indicated by the following symbols: *460-nm light vs. no light; ○ 550-nm light vs. no light; and ▽, 460-nm light vs. 550-nm light. The pre-light exposure episode represents a 2-h dark adaptation episode under zero lux, whereas the light level in the 1.5-h post-light exposure was 2 lx. Taken from Cajochen et al.[51] with permission.

of short-wavelength light (460 nm) in the evening.[64] In the second study, pupil-dilated subjects were exposed to the same wavelength and intensity of light as used in[60] but for a longer exposure time (6.5 h) timed to start 9.25 h before usual waketime (i.e., during the biological night).[61] Compared to the 555 nm light, significantly lower sleepiness ratings were observed in the 460 nm light condition, which was paralleled by decreased auditory reaction times, fewer attentional failures, decreased EEG power density in the delta–theta range and increased EEG power density in the high-alpha range but no effects on cortisol.[61] In the third study by Revell et al. [62] five different wavelengths (420, 440, 470 and 600 nm) were compared. Interestingly, their findings suggested that the spectral sensitivity of the effect of low irradiance light on subjective alertness is maximal at very short wavelengths (~420 nm). Unfortunately, the authors used subjective sleepiness ratings as the only dependent variable and no further central or autonomic measures of sleepiness. Different numbers of subjects participated in the five light conditions, and no pre- and after light exposure sleepiness ratings were taken, all of which leave the authors' conclusion that human non-visual responses may differ in their spectral sensitivity reflecting differences in the photoreceptors a little bit speculative. However, their suggestion that non-visual responses need to be assessed individually, and that the photic properties of one particular non-visual response cannot be generalized is most likely to be true but needs further confirmation. In the last study, a recent fMRI protocol,[63] blue light (470 nm) elicited greater non-image forming responses than green (550 nm) monochromatic light in brain areas, which are involved in working memory and implicated in the modulation of cognition by arousal (i.e., left thalamus). Thus, besides alertness even brain structures involved in higher cognitive functions are modulated by light, possibly through the melanopsin photoreception system.

This latter finding adds to a number of many non-visual light responses in humans, such as melatonin suppression,[51] circadian phase shifting,[65] cone electroretinogram,[66] pupillary constriction,[60] sleep latency,[67] nocturnal decline in EEG slow-wave activity,[68] elevation of heart rate and core body temperature as well as circadian gene expression (PER2) in the oral mucosa.[64] Common to all of these responses is that they are more sensitive to short wavelength light and may thus be modulated by melanopsin-based photoreception. However, a definitive answer would be to investigate people lacking the classical receptors, or having a melanopsin deficiency, and to see any repercussions this may have on light-induced changes in alertness and the above-mentioned responses. Also, the use of short wavelength "knockout" light sources as a control would help in clarifying to what extend rods and cones are still involved in the non-visual effects of light in humans.

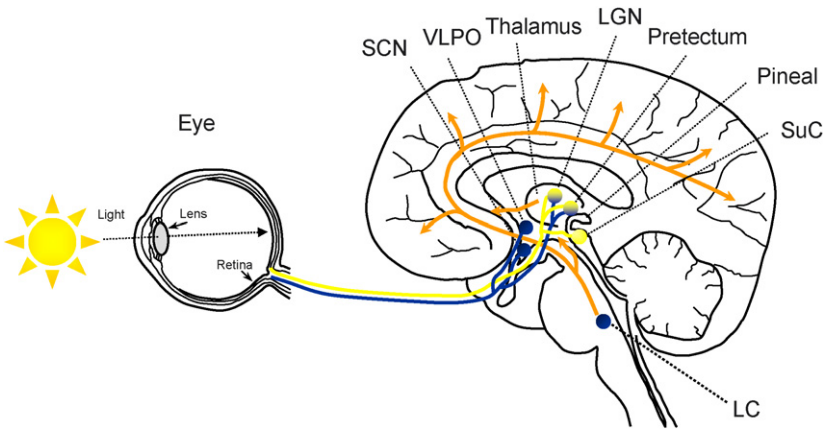

Figure 5 Pathways for light-induced activation of non-visual brain areas. Light exposure activates melanopsin-containing intrinsically photosensitive retinal ganglion cells and rod and cone-driven classical ganglion cells. Melanopsin-containing ganglion cells (blue) project to a range of 'non-visual' areas of the brain, including the suprachiasmatic nuclei (SCN), which then project multisynaptically to the pineal gland, as well as to many areas that share input from the visual photoreceptor system (yellow), such as the lateral geniculate nucleus (LGN), pretectum and superior colliculus (SuC). Through as yet unidentified pathways, light stimulates the ascending arousal system and eventually the cortex to enhance alertness and cognition. Furthermore, light information also reaches sleep-promoting neurons of the ventrolateral preoptic nucleus (VLPO)[14] and the noradrenergic locus coeruleus (LC) system, which is implicated in the circadian regulation of arousal.[61] Adapted from Saper et al. [60] and Lockley and Gooley.[84]

In terms of brain anatomy, a number of key candidate brain regions may be involved in lights' non-image forming action. Melanopsin-containing intrinsically photosensitive retinal ganglion cells project to a range of non-visual areas of the brain, including the SCN, which then project multisynaptically to the pineal gland, as well as to many areas that share input from the visual photoreceptor system, such as the lateral geniculate nucleus, pretectum and superior colliculus (Figure 5). Through as yet unidentified pathways, light stimulates the ascending arousal system and eventually the cortex to enhance alertness and cognition.[69] In this context, two brain regions are of particular interest: the ventrolateral preoptic nucleus (VLPO) in the anterior hypothalamus and the locus coeruleus (LC) located in dorsal tegmentum of the pons. Results from animal studies have recently confirmed that both the VLPO and LC are involved in the regulation of the sleep-wake cycle.[69,70] The VLPO is directly innervated by melanopsin-positive retinal ganglion cells[71] and contains sleep-promoting neurons,[69] which potentially can be inhibited by light and thus prevent sleep. The VLPO innervates all of the major nuclei of the ascending monoaminergic and in particular the histaminergic pathways, which are thought to play a key role in wakefulness and EEG arousal.[72,73] Besides, the noradrenergic LC system regulates the amplitude of the sleep-wake circadian rhythm set by the SCN by increasing wakefulness during the active period.[70] Light deprivation induces a loss of noradrenergic fibres, which in turn decreases the amplitude of the sleep-wake-rhythm. On the other hand, periodic light stimulation is necessary for the LC in entraining the sleep-wake rhythm.[70] Recent human data suggest an important role of the thalamus and of the insula during and after prolonged exposure to light in nonvisual responses to light.[42,44]

Clinical and non-clinical application

Light is the first choice to treat winter depression.[85] Seasonal Affective Disorder (SAD) is a form of depression in which symptoms typically recur every year during the shorter days of autumn and winter and remit during the longer days of spring and summer. Symptoms include low mood, reduced interest, decreased concentration, low energy, and fatigue. Other clusters of symptoms are often present, including an increased need for sleep, increased appetite and carbohydrate craving with resultant weight gain (for a review see Ref. [74]). The incidence of subsyndromal SAD (sSAD), characterized by similar symptoms without meeting the full criteria for major depression, is reported to be up to three times as prevalent as SAD (~30% of the population).[75] Although the etiology and pathophysiology remain uncertain, light therapy has proven to be an effective therapeutic intervention for patients of all ages with both SAD and sSAD.[74] Whether the mood enhancing effect of light is also related to its alerting property is unclear, since the mood improving effect of a 5-day light therapy regimen followed by a 40-sleep deprivation, which itself was antidepressant, was not paralleled by corresponding changes in subjective alertness.[76] However, the circadian phase shifting capacity of light, particularly in the morning, has often been reported to be crucial for its antidepressant effect. Although a circadian rhythm phase advance often accompanies the antidepressant response to early morning light exposure, advances also occur in partial responders and non-responders and thus might be an epiphenomenon. One needs to show that the size of the phase advance correlates with the magnitude of improvement. Thus far, this has been demonstrated only by Terman and colleagues.[77] In a protocol with 10,000-lx treatment for 30 min on habitual awakening, the magnitude of antidepressant response was negatively correlated with the interval between evening melatonin onset and morning treatment time. To maximize the likelihood of a treatment response, the authors recommend initiating morning light no later than 8.5 h after a patient's melatonin onset.[78]

As for the alerting effect of light, its wavelength may also play an essential role in the antidepressant response. Narrow-band blue light was recently tested against dimmer narrow-band red light panels (an intended placebo light) for clinical efficacy in treating SAD.[79] Although narrow band blue light therapy showed promise as an effective treatment for SAD, this study did not establish narrow band blue light as uniquely effective for SAD. Whether there is a therapeutic advantage to narrow-band green over white illumination requires further study, particularly regarding their tolerability and adverse effects.

Beyond SAD, light therapy appears promising as a treatment for other major depressive disorders: non-seasonal (recurrent, chronic), premenstrual, antepartum, postpartum depression, depression associated with bulimic symptoms, and seasonal manifestations of adult attention-deficit disorder (for a review see Ref. [78]).

In addition to the treatment of clinical sleep and mood disorders, the utility of light for resolving problems associated with intercontinental travel (jet lag), shift work and space flight is currently being evaluated. Common to these problems is a

misalignment between the internal circadian pacemaker and the external environment. In the long term, this circadian dysregulation may contribute to health problems such as cardiovascular disease, diabetes, sleep disorders, gastro-intestinal disorders and possibly cancer.[80] Light regimes can be used to reset the pacemaker or prevent desynchronization in potentially hazardous environments (e.g., shift work). For some situations (e.g., rapidly rotating shifts, the normal office environment) it is probably better to base the timing of light exposures towards improving alertness without phase shifting.[81,82] However, given that there is no dead zone for phase shifting the circadian system in humans,[65] it is not conceivable to enhance alertness with light without affecting circadian phase.

Thus, besides the circadian properties, the acute alerting and performance enhancing effects of light are becoming more and more important for the design of indoor light standards in architectures, since many current office lighting may not satisfy the non-visual lighting criteria. Vertical illuminances of >1000 lx was measured in only 20% of offices in a large study by Ariës.[83] In this study, people who worked under lower vertical illuminance levels reported significantly more fatigue and worse sleep quality than people working under high levels of vertical illuminance, also when adjusted for gender, age, eye correction, seasonal sensitivity and chronotype.[83]

Visual performance, visual comfort and aesthetic enhancement of the built environment have traditionally been the primary focus of architectural lighting strategies. It is now time to consider non-visual effects of light in architectural designs. The current knowledge has considerably accumulated in the recent past to warrant recommendation on how to best utilize light in order to support, rather than disrupt, the natural environmental light-dark cycle and thus human alertness levels and biological rhythms.

Conclusions

The alerting action of light in humans has received little attention so far. Since the discovery of the non-image forming photoreceptor system and its connection to neural circuits implicated with alertness regulation, the investigation of the alerting properties of light in humans has just started. Recent studies confirm the potential role the non-image forming system has for alertness. This may lead to new approaches to prevent and treat undesirable sleepiness and performance decrements during the early nighttime hours in some subject populations, such as older people, as well as nighttime sleepiness and performance decrements in night shift workers and after jet lag. Knowledge about the non-visual effects of light will also help to design and implement potentially successful novel light devices and light exposure schedules in the work place environment.

Practice points

1. Light exerts powerful non-visual effects on a wide range of biological functions including the modulation of human alertness levels.
2. Factors such as the dose (illuminance levels), exposure duration, timing and wavelength of light have important repercussions on the alerting response to light in humans.
3. Light-induced brain activation is governed by neural circuitry involved in the regulation of sleep/wake states.
4. Both the ‘‘light behavior’’ and ophthalmologic status must be considered in treating patients suffering from daytime sleepiness and chronic fatigue syndrome.

Research agenda

1. Emerging evidence indicates a potential role of the non-image forming system for the regulation of alertness. This opens an exciting area of research that will lead to improved understanding on how retinal and suprachiasmatic networks are involved in the regulation of circadian rhythms and sleep/wake homeostasis.
2. To state that melanopsin is the photopigment responsible for all non-image forming responses is not correct until one shows no evidence that blue cones, or a combination of several photoreceptors, are in part responsible for the non-image forming responses observed.
3. Further research is needed to define the light levels in the working environment necessary to ‘‘satisfy’’ the circadian clock and/or ‘‘non-visual’’ physiology.

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