Lighting up the clock
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Chapter 8

General discussion

Melanie Rüger
8. General discussion

The main aim of the work presented in this thesis was to gain a better understanding of the effects of bright light on human performance and well-being in order to optimize its applications. Four experiments were carried out, in which different light stimuli were applied to study their effect on human functioning and the underlying physiological mechanisms. Below I discuss the results and their implications, first with a focus on the circadian effects, then with a focus on the immediate effects of light.

8.1 Circadian effects of light

The question what kind of light stimulus is needed to induce circadian phase-shifts, i.e., to entrain the biological clock, was brought into renewed focus of chronobiology by Campbell and Murphy (Campbell and Murphy, 1998). The authors claimed that exposure of the popliteal area (back of the knee) to bright light induces phase shifts in the circadian rhythms of melatonin and core body temperature. The existence of such a non-visual pathway for resetting the circadian pacemaker would enable us to study the effects of bright light on the circadian system without confounding placebo or expectation effects of subjects and patients, as the light stimuli might be presented without the subject being aware of the light.

Based on these considerations we tried to replicate the findings of Campbell and Murphy. We failed to find any phase-shifting effects of extraocular light exposure on core body temperature, melatonin, and sleepiness (chapter 2). These results are in accordance with a series of other studies that also tried to replicate extraocular phototransduction in humans (Eastman et al., 2000; Koorengevel et al., 2001; Lindblom et al., 2000b; Wright, Jr. and Czeisler, 2002; Lushington et al., 2002). All attempts failed, and therefore we conclude that there is no extraocular phototransduction in humans. The fact that bright ocular light delayed the CBT rhythm and the melatonin rhythm within the same study is additional proof that a light stimulus needs to be perceived by the eye in order to induce changes in the biological clock. This is further in agreement with experimental studies in bilaterally enucleated mammals that also demonstrated the absence of extraocular light perception in entrainment (Yamazaki et al., 1999; Meijer et al., 1999).

The conclusion drew the attention back to the eyes as the essential sensory organ to perceive the light timing signal. This shift back to the eye occurred at about the same time when Berson et al. (Berson et al., 2002) and Hattar et al. (Hattar et al., 2002) had
discovered that rods and cones are not the only photoreceptors in the retina. A special type of retinal ganglion cells, containing melanopsin as the photopigment (Melyan et al., 2005; Qiu et al., 2005) serves as luminance detector, and provides this information to, for instance, the pupillary contraction mechanism and the circadian pacemaker (Lucas et al., 2003).

We exploited the spatial asymmetry in the retinal illumination effects on melatonin suppression to address the question whether the same photoreceptors are responsible for immediate melatonin suppression and for circadian phase-shifting in humans (chapter 6). By applying proper shielding, we illuminated only part of the retina, either the nasal part or the temporal part. This induced a significant phase-shift in the melatonin rhythm under nasal illumination, not under temporal illumination. Circadian phase-shifts could be detected neither in the rhythm of core body temperature nor in the alertness rhythm with illumination in either part of the retina. The caveat here is that the experimental design allowed the detection only of immediate, first cycle phase shifts, not the steady state effects after many cycles in constant conditions. It may also be that a group size of 11 subjects is not large enough to show effects in the variables core body temperature and alertness, which show large inter-individual variability (Klerman et al., 2002). The fact that both melatonin suppression and phase shift of Dim Light Melatonin Onset (DLMO) were greater following nasal than temporal illumination suggest nonetheless that there is a functional divergence between nasal and temporal areas of the human retina, maybe due to differences in melanopsin ganglion cell density. The possibility of a functional differentiation between nasal and temporal retina may well provide another opportunity to study the effects of light on the biological clock without confounding placebo effects as subjects and patients would not know which part of the retina are expected to induce certain changes and which are not. They would consciously see the stimulus in both cases. Certainly, further investigations of such a functional differentiation are of interest, although large subject groups will be required and the experimental set-up would need to be made more user-friendly while still allowing for appropriate control over exposed areas. For now, we conclude from our findings that nasal illumination with 100 lux of bright white light through dilated pupils is able to induce a phase shift in DLMO, but not strong enough to induce a phase shift in core body temperature and alertness.
8.2. Immediate effects of bright light

Even if extraocular light fails to induce circadian phase-shifts, it could still be able to influence physiological and psychological states of humans in an acute fashion. Therefore in our investigation on extraocular illumination we compared the changes during the 4 hours of extraocular light exposure to those during ocular light exposure (chapter 2). No immediate effects of extraocular light were found, whereas bright ocular light exposure on the whole retina reduced the nocturnal circadian drop in CBT, suppressed melatonin, and reduced sleepiness significantly. Our results are in accordance with the results of several other studies (Lockley et al., 1998; Rogers et al., 1999; Hebert et al., 1999; Jean-Louis et al., 2000; Lindblom et al., 2000a; Wright, Jr. and Czeisler, 2002) which also failed to suppress melatonin by exposure to extraocular light. We conclude that a light stimulus must be perceived by the retina in order to acutely enhance core body temperature, suppress melatonin, and reduce subjective sleepiness.

Following up on these white ocular light studies, we explored further whether the extent of melatonin suppression and sleepiness reduction varies with the light’s wavelength. In a quasi-field setting we exposed a large group of sleep deprived subjects to approximately 100 lux of blue or red light during the nighttime and measured melatonin suppression and subjective sleepiness. Melatonin suppression and reduction of sleepiness were greater under blue light compared to red light (chapter 3). The fact that melatonin suppression is particularly sensitive to blue light is consistent with findings of others (Brainard et al., 2001; Thapan et al., 2001; Wright and Lack, 2001; Lockley et al., 2003; Warman et al., 2003; Figueiro et al., 2004; Herljevic et al., 2005). The fact that also sleepiness is more reduced under blue light than under red light (see also Cajochen et al., 2005) may well be due to the involvement of the blue-sensitive ganglion cells recently discovered in the retina, which contain the photopigment melanopsin (Foster, 2005).

This work led to further questions concerning the immediate effects of light on melatonin suppression and reduction of sleepiness: Does the retinal area of illumination contribute to the size of the alerting effects of bright light? We illuminated either the nasal or the temporal part of the retina with white light and measured melatonin and subjective sleepiness at hourly intervals (chapter 6). In contrast to the study by Visser et al. (1999), we dilated the pupils of our subjects with cyclopentolate in order to control for differences in pupil size. To compensate for the lack of attenuation of light intensity by the pupil, we reduced the used stimulus from 5000 to 100 lux of bright white light. With a clear suppression of melatonin due to both nasal
and temporal illumination of the retina, including the greatest melatonin suppression in the nasal condition, we fully confirmed the findings of Visser et al. (1999). Moreover this showed that those results did not depend on differences in pupil constriction. We failed to show the same effect for subjective sleepiness. Subjective sleepiness was neither reduced by nasal nor by temporal illumination of the retina with light of this reduced intensity. Similarly, core body temperature was unaffected by the two different illumination conditions. This might be due to the fact that the stimulus was not strong enough to induce immediate changes in these two variables. In summary the results show that the suppression of endogenous melatonin during the nighttime can be induced by ocular light stimuli of different intensities and that the extent of melatonin suppression depends on wavelength and area of retinal exposure and, in case of nasal and temporal illumination, this is not accompanied by a reduction of sleepiness.

This is in contrast to the common observation that light induces simultaneous changes in physiology (melatonin suppression, elevation of core body temperature) and psychology (reduction of subjective sleepiness) during the nighttime (Badia et al., 1991; Daurat et al., 1993; Campbell et al., 1995; Cajochen et al., 2000; Kubota et al., 2002). This divergence led to the question to what extent the effects of ocular light exposure are time-of-day-dependent? For this purpose we compared the effects of 4 hours of bright white ocular light exposure during the nighttime to the same light treatment given during the daytime, exactly 12 hours out of phase (chapter 4). The nighttime light exposure was scheduled at the circadian phase where the Phase Response Curve (PRC) predicts maximal phase shifting effects, and where also melatonin concentration is high (from midnight until 4 a.m.). The daytime light exposure falls at a phase where no circadian effects are expected and melatonin is virtually absent (from noon until 4 p.m.). Surprisingly both nighttime and daytime exposure to bright ocular light reduced sleepiness in independent groups of subjects, whereas changes of the physiological measures, i.e. increased heart rate and enhanced core body temperature, only occurred during the nighttime bright light exposure. Apparently the suppression of endogenous melatonin and the enhancement of core body temperature are no prerequisites for light to elicit its activating effects.

If this holds true for the subjective sleepiness, does it also hold true for performance measures which are known to decrease as subjective sleepiness increases (Dinges et al., 1997; Lamond and Dawson, 1999; Rogers et al., 2003) and is there an EEG-based explanation for this? On the basis of the recordings of three different performance measures (an addition task, a letter cancellation test, a simple reaction time task) we showed that ocular bright light exposure relative to dim light is able to
increase performance irrespective of time of day (chapter 5). Apparently bright light prevented subjects from falling asleep, which is reflected in the overall effect of bright light on the 3-4.5 Hz bin (in the delta or slow wave band). The similarity of the performance and sleepiness effects irrespective of the time of day was not reflected in the alpha and the theta power of the wake-EEG. Only the nighttime data supports the idea that low power in the alpha frequency range of the wake EEG predicts low performance and that this can be counteracted by bright light exposure. During the daytime bright light exposure reduces sleepiness and improves performance just as during the night, but does not affect alpha power. The absence of a significant effect on theta power (5-5.5 Hz) is not consistent with the existing literature (Cajochen et al., 2000), which might be due to differences in the method used (eyes open versus eyes closed) or in the data analysis. The conclusion for Part II is that the relationships between physiological measures, such as melatonin suppression, change in body temperature and alpha activity in the wake EEG, with psychological measures such as sleepiness and performance are more complex than commonly presumed and that the alerting effects of light can not be understood on the basis of those physiological variables alone.

The alerting properties of bright light are a major reason for the growing interest in bright light application. For optimizing the use of bright light in different settings and for different purposes, ranging from winter depression therapy to optimization of working environment, it is crucial to know more about the mechanisms that lead to the alerting effects. Since melatonin has frequently been proposed to mediate part of the effects, the relationship between reduction of sleepiness and suppression of melatonin is of interest. We compared and correlated the datasets on melatonin and sleepiness/fatigue obtained in chapter 2, 4, and 5. The results clearly indicate that there is only a weak relationship between suppression of melatonin and the reduction of sleepiness/fatigue. Several other physiological variables have been suggested to influence sleepiness. Kräuchi and colleagues (Kräuchi et al., 1998; Kräuchi and Wirz-Justice, 2001) have demonstrated a functional link between the degree of heat loss (distal vasodilatation) and subjective sleepiness (measured by the KSS). We were not able to detect such link in the daytime study. We found no relationship between changes in sleepiness and changes in core body temperature. Alternative explanations for the way light elicits its activating and alerting properties in humans are clearly needed. This leads us back to neuroanatomic studies in mammals, which provide the possibility to identify possible projections from the SCN to other brain areas involved in regulatory processes such as the sleep-wake cycle.
Aston-Jones et al. (Aston-Jones et al., 2001) showed indirect projections from the SCN to the locus coeruleus (LC), relayed via the dorsomedial hypothalamic nucleus (DMH). By performing lesions of the DMH, which eliminated circadian variations in the LC, they proved the functionality of this circuit. The locus coeruleus itself is associated with arousal and sleep-wake regulatory processes and cognitive performance (Aston-Jones and Bloom, 1981; Usher et al., 1999; Aston-Jones et al., 2000). Furthermore, Deurveilher and colleagues (Deurveilher et al., 2002; Deurveilher and Semba, 2005) showed that the medial preoptic area, the subparaventricular zone, and the dorsomedial hypothalamic nucleus might not only serve as relays to sleep-promoting nuclei such as the ventrolateral and the medial preoptic nuclei, but also to arousal-regulatory brain areas such as the locus coeruleus. Saper and colleagues (Saper et al., 2005) associate certain neurons within the subparaventricular zone to certain circadian rhythms. In particular they show that neurons in the dorsal subparaventricular zone are involved in regulating body temperature rhythms whereas neurons within the ventral part of the subparaventricular zone are responsible for circadian rhythmicity in sleep and wake. These latter neurons project back to the dorsomedial hypothalamic nucleus, which serves as a relay itself to further sleep-wake regulatory centers as Deurveilher et al. (2002, 2005) showed. Chou and colleagues (2003) proved the importance of the DMH in circadian rhythmicity by means of lesion studies in rats. They found severe reductions in rhythms in feeding, locomotor activity, but most importantly in sleep-wakefulness. This is of importance as the DMH projects directly and indirectly to the ventrolateral preoptic nucleus (Chou et al., 2003). Interesting in this context is the fact that Lu et al (Lu et al., 1999) identified a set of sleep-active cells in the ventrolateral preoptic nucleus of rats that receive direct luminance signals from the retina. The ventrolateral preoptic nucleus also belongs to the target regions for the projections from intrinsically photosensitive retinal ganglion cells, which contribute to circadian entrainment, pupillary light reflex, and the regulation of sleep-wake states (Gooley et al., 2003). In humans, the locus coeruleus is one of the candidate nuclei that is influenced by bright light exposure during the nighttime as Perrin and colleagues (Perrin et al., 2004) showed in their PET study, using regional blood flow as an activation-deactivation marker of brain areas. Additional proof for the similarity between the SCN-projections found in rodents and humans comes from post-mortem studies in humans, that showed projections from the SCN to the DMH and from the DMH to the paraventricular nucleus of the thalamus and the ventral medial hypothalamus, which is part of the endocrine signal transmitting axis from the SCN to the body organs (Dai et al., 1998a; Dai et al., 1998b; Buijs et al., 2003). Integrating the neuroanatomical evidence with our own findings on the weak relationship between
melatonin suppression and reduction of sleepiness leads to the speculation that the indirect projections from the SCN to brain areas strongly associated with the regulation of sleep-wake, like the ventrolateral preoptic nuclei (VLPO) are more likely to play a role in the alerting effects of bright light.

This prospect of the possible neuroanatomic basis of light-induced SCN projections to sleep and arousal regulating brain areas, leads us back to the initial goal of this thesis: Gaining a better understanding of the effects that bright light has on human well-being in order to optimize its applications. The use of bright light as a remedy for several complaints (jet-lag, shift-work) and diseases (winter depression, major depression) has led to a growing need for a better understanding of the fundamental aspects of bright light. The general conclusions drawn from the results of this thesis are: a) only bright ocular light is able to induce immediate and phase-shifting effects in human circadian physiology (chapter 2), b) the effects of ocular bright light on physiological and psychological variables are wavelength-dependent (chapter 3) and time-of-day-dependent (chapters 4 and 5), c) the amount of melatonin suppression depends on the retinal area that is exposed (chapter 6), and d) the suppression of endogenous melatonin is not a prerequisite for the reduction of subjective sleepiness in humans (chapters 4 and 7).

8.3 Perspective

The knowledge that bright light exposure can influence psychological states without inducing changes in the physiological variables we have recorded, as seen during daytime bright light exposure, has important consequences for the application of light. It tells us that even light stimuli of the same intensity are not the same, as they have different effects depending on their time of application. This emphasizes the importance of being aware of what one wants to achieve by using bright light. Which states of well-being and functioning do we want to induce in which group of people and what kind of light do we than have to use?

What are beneficial effects of bright light during a nightshift, i.e. reduction of sleepiness and increase performance (Lowden et al., 2004), may be counterproductive for re-adaptation to the normal day-night rhythm as we know that bright light suppresses melatonin and shifts circadian rhythms (e.g. Rüger et al., 2003). An interesting approach to this dilemma is taken in a study by Kayumov et al. (2005) that explores the use of short-wavelength blocking goggles during the night which prevented the light induced melatonin suppression without affecting performance.
Combining fundamental research on the basis of the beneficial effects of bright light with the invention of user-friendly solutions will become a central aspect in the future of light therapy and application.

References


