Lighting up the clock
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Chapter 1

General introduction

Melanie Rüger
1. General introduction

Our daily functioning varies systematically across the 24 hours of the day. On the one hand this is caused by circadian variation of physiological and behavioral rhythms such as the rhythm of core body temperature, the sleep-wake cycle or the 24-h rhythm of alertness. On the other hand, the variation in functioning itself elicits 24-h fluctuations in physiology and behavior. These 24-h rhythms are synchronized or “entrained” to the environmental light-dark cycle. The neuroanatomic structure keeping track of the changes in light and generating the rhythms with a period of approximately 24-h is called the “biological clock” and is localized within the suprachiasmatic nucleus (SCN) beneath the thalamus of the brain. When the biological clock runs out of phase with external time, we experience complaints such as increased daytime sleepiness, sleep disturbances, and reduced performance known from phenomena such as jet lag, shift work, and several circadian sleep disorders (Dinges, 1995; Rajaratnam and Arendt, 2001). The most important signal to keep the biological clock, and therefore ourselves, entrained to the external world is light, which is transmitted from the retina via the retino-hypothalamic tract to the SCN. From the SCN the timing signal is then transmitted by means of hormones and neural projections, and serves to keep the circadian rhythms of behavior and physiology intact (Klein and Moore, 1991; Buijs et al., 2003). In humans, the pineal hormone melatonin is one of the internal messenger signals that helps internal rhythms to maintain synchrony with the environmental light-dark cycle. Melatonin is exclusively secreted during the subjective night, and its plasma level rises during the evening and drops off in the early morning (Arendt and Skene, 2005).

Light has long been known to synchronize human circadian rhythms (Aschoff et al., 1969; Wever, 1980; Czeisler et al., 1989). Very recently separate specialized photoreceptor cells have been discovered in mammals that subserve this synchronization to a large extent. Besides the classical visual photoreceptors of rods and cones, the mammalian retina contains a third kind of photoreceptor called “circadian photoreceptor”. Animal studies proved these circadian photoreceptors to be ganglion cells (iRGCs) that are intrinsically photosensitive and integrate light information over time and space. Therefore they serve as irradiance detectors participating in the entrainment of the circadian system, but also in the pupillary light reflex, and in the suppression of melatonin (Lucas et al., 1999; Berson, 2003; Hattar et al., 2003). In humans evidence for the existence of a circadian photoreceptor comes from studies that established an action spectrum for light-induced melatonin suppression. The action spectrum best compares to a rhodopsin template, peaking
around $\lambda_{\text{max}} = 459$ nm, instead of at 555 nm as would be the case if the cone system was responsible (Thapan et al., 2001; Brainard et al., 2001a; Brainard et al., 2001b). The discovery of the intrinsically photosensitive ganglion cells generates new research questions, such as: How are the circadian photoreceptors distributed across the human retina? Are the same photoreceptors that are involved in the immediate melatonin suppression also responsible for phase-shifts of the circadian pacemaker (Lasko et al., 1999; Visser et al., 1999; Glickman et al., 2003)?

The main question of this thesis is how bright light affects physiological and psychological states of humans. The variables we measured and present here reflect both aspects. The major physiological output variables presented in this thesis are: melatonin, core body temperature, heart rate, electroencephalogram, and cortisol. For these parameters it is well established that they vary with a period of circa 24 hours, and that they are also sensitive to immediate light induced changes (Wever, 1980; Khalsa et al., 2003). The light-induced changes and the circadian variation of psychological states are reflected in the measures of subjective sleepiness, alertness, fatigue, and performance (Campbell and Dawson, 1990; Dijk et al., 1992; Campbell et al., 1995; Cajochen et al., 2000). The stimulus investigated in this thesis is light. We varied the light intensity, the wavelength, the timing of light exposure, and we varied the exposed area of the retina. Light intensity is commonly measured in lux, a measure based on the spectral sensitivity distribution of rods and cones. It is a useful measure to compare stimuli of equal spectral composition or to compare the effects of stimuli with presumed equivalent effects on the visual photoreceptors. Concerning light intensity we applied “dim” light and “bright” light. Obviously, “dim” and “bright” are relative measures. In comparison to normal indoor light (~ 200-300 lux) 5000 lux is bright, and 10 lux is dim. Against a clear sky on a sunny day in summer (~ 100,000 lux) 5000 lux is still rather dim. 100 lux of light intensity would normally be rather dim, but upon pharmacological pupil dilation it will be rather bright.

Once the light signal is perceived, it can influence the well-being of humans in two distinct ways. It can immediately change the level of the physiological and psychological parameters (a non-circadian effect) or it can induce a phase shift in the circadian pacemaker influencing these parameters, in the SCN. Below I summarize first the immediate effects of bright light, then the circadian effects, followed by the scope of this thesis.
1.1. Immediate (non circadian) effects of light

Apparently light has an immediate alerting and activating effect on humans. Most of us share the experience that staying awake during a lecture in a dark room is more difficult than in a brightly lit room and that turning on the lights has an immediate effect on our feeling of alertness. This alerting and activating effect of light has been studied mostly in the context of prolonged wakefulness during the night. Within this context we now know that light suppresses melatonin in an acute fashion (Lewy et al., 1980), enhances core body temperature (Badia et al., 1990; Badia et al., 1991), and reduces sleepiness (Campbell et al., 1995; Cajochen et al., 2000). The magnitude of melatonin suppression seems to depend both, on the wavelength of the light stimulus and on the area of the retina that is exposed to light. Concerning the wavelength, studies in animals and humans proved that exposure to light of the blue-green spectrum yields the greatest melatonin suppression (Lucas et al., 2001; Wright and Lack, 2001; Foster, 2005). This is due to the blue-sensitivity of the intrinsically photosensitive ganglion cells in the retina (Berson et al., 2002; Hattar et al., 2002). In addition, Gooley and colleagues (2003) showed that these cells have projections to brain areas, such as the subparaventricular zone (SPVZ) or the ventro-lateral preoptic area (VLPO), brain areas associated with sleep-wake regulation (Lu et al., 1999). Does the fact that blue light yields the greatest melatonin suppression via photosensitive ganglion cells that project to sleep-wake-regulatory brain areas, also lead to a greater reduction of sleepiness under blue light? This question will be addressed in chapter 3, where the effects of blue light on melatonin suppression and sleepiness are compared to the effects of red light.

The findings on melatonin suppression due to illumination of different areas of the retina in humans are inconsistent and vary greatly in methodology (Adler et al., 1992; Lasko et al., 1999; Visser et al., 1999; Glickman et al., 2003). We have attempted to replicate and further explore the findings of Visser et al. (1999) in chapter 6. A further interesting aspect of the effects of bright light is that in most of the studies the reduction in subjective sleepiness was accompanied by the suppression of melatonin and/or the enhancement of core body temperature in a dose-dependent manner (Cajochen et al., 2000). Melatonin suppression has therefore been considered a causal factor in the alerting mechanism of bright light (Badia et al., 1993; Gilbert et al., 1999; Lucas et al., 2003). Much less is known about the effects of bright light exposure during the daytime, i.e., at times when melatonin is virtually absent. Several studies have indicated time-of-day-dependence of the effects of bright light in humans on sleepiness, performance, and the wake-EEG (Badia et al., 1990; Badia et al., 1991;
Daurat et al., 1993; Leproult et al., 1997; Phipps-Nelson et al., 2003). This leads to the question: What are the activating and alerting effects of bright light during the day on human psychophysiology (chapter 4), performance and the wake-EEG (chapter 5)? By comparing the data obtained at night with those obtained in the daytime it would be possible to increase our knowledge about the role of melatonin and its suppression in the regulation of subjective sleepiness and fatigue (chapter 7).

1.2. Circadian effects of light

In addition to the immediate activating effects of light, light can also cause slow and longer lasting effects on physiology and psychology. Most of us will have experienced the discomforting effects of misalignment between our biological clock and our behavior, for instance due to traveling across time zones (jet-lag) or to extended wakefulness during night- or shift work. Indeed the function of the biological clock or “pacemaker” is entrainment, i.e., to keep the organism’s behavior synchronized to the environmental light dark-cycle and by this to help the organism to anticipate desired future activity (Pittendrigh, 1981; Czeisler et al., 1989; Daan and Aschoff, 2001). As the source of increased daytime tiredness, reduced alertness, sleep and gastro-intestinal problems, the mismatch of internal and external time in behavior can lead to severe accidents and national catastrophes as seen in Three Miles Island and Chernobyl (Dinges, 1995; Rajaratnam & Arendt, 2001). Light is the prominent signal to entrain the pacemaker and therefore it can also be used to shift the clock deliberately. Thus, depending on the phase in the circadian cycle, one can shift the rhythms of core body temperature, melatonin secretion, and alertness forwards or backwards in time and therefore influence physiological and psychological states in humans. Animal as well as human studies helped to establish so-called phase-response curves (PRCs), which summarize the results. Light in the evening produces a phase delay of the circadian pacemaker, whereas light in the morning will result in a phase advance (Honma and Honma, 1988; Minors et al., 1991; Beersma and Daan, 1993; Khalsa et al., 2003). Maximal responses to bright light are observed during the night. While the phase shifting effects of bright light are commonly acknowledged, the effects of extraocular light have long remained controversial (Campbell and Murphy, 1998; Wright, Jr. and Czeisler, 2002). The idea of the eye being the only organ in mammals able to detect light information was challenged by a study of Campbell and Murphy (1998), in which the authors claimed that humans, as some other vertebrates like lizards (Foster and Soni, 1998; Campbell et al., 2001), in addition of having ocular photoreception, could make use of extraocular phototransduction pathways. In particular they proposed that
illumination of the circulating blood (realized in practice by illuminating the skin at the back of the knee, the popliteal area) in humans would yield circadian phase shifts. The presence or absence of such a non-visual pathway would have a major influence on our understanding of the circadian system. Hence, we, as well as other groups have attempted to replicate this finding in chapter 2 by comparing light exposure of the back of the knee versus the whole retina with undilated pupils.

The daily fluctuations in functioning, such as in performance and alertness, are not only due to the biological clock or to current light exposure. Another major influence on performance and alertness is the duration of prior wakefulness and prior sleep. In most of the studies presented in this thesis, sleep timing was virtually identical for all subjects in the study. As a result sleep timing by itself cannot have caused the results of the studies. However, if we compare responses to light during the night with responses to light during the daytime (chapters 4 and 5), we must consider the possible influence of the difference in prior sleep/wake history. In principle there are two ways to do that. One is to take the differences for granted and compare the changes in the variables induced by the light, under the assumption that the changes in alertness and performance are less influenced by prior sleep-wake times than the absolute levels. This method is used in our studies. Another method is to first shift sleep timing to other times of day to achieve similar prior sleep-wake history for the two situations to be compared. The suitable protocol for this is the forced desynchrony protocol (Dijk et al., 1992; Hiddinga et al., 1997). During this protocol subjects are scheduled to rest-activity cycles that are either longer or shorter than 24-h, therefore their sleep episodes are gradually shifted over all circadian phases. The inability of the pacemaker to follow these alternations in sleep-wake periods leads to a desynchronisation between the pacemaker and the sleep-wake-cycle, and hence to the possibility to disentangle their contributions to the rhythms of alertness, performance and mood. Results from such forced desynchrony studies showed that over the first 0-16 hours of wakefulness, alertness and performance remain fairly stable, whereas during wakefulness exceeding 16 hours or longer, they will begin to deteriorate (Dijk et al., 1992; Boivin et al., 1997). Under conditions of forced desynchrony, Dijk et al. (1992) showed that the circadian regulation of alertness and performance was closely associated with the rhythm of core body temperature. In chapter 2 we test whether such strict relationships can also be observed upon a light induced phase shift of the circadian pacemaker when sleep timing is kept constant. Evidence from animal and human studies indicated that the circadian photoreceptors, responsible for melatonin suppression, might not be evenly distributed over the retina (Cooper et al., 1993; Provencio et al., 2000; Hannibal et al., 2002; Berson et al., 2002; Hattar et al., 2002). A major question is what function could
be served by the uneven distribution of the photoreceptors. In chapter 6 we test whether it is likely that the same receptors responsible for immediate melatonin suppression are also responsible for the phase-shifts.

1.3. Scope of the thesis

In recent years we have seen a steady increase in the use of bright light, for instance in therapy to alleviate symptoms of winter depression, in the treatment of sleep disorders, improvement of the work environment of shift workers, or the reduction of jet-lag complaints. Fundamental knowledge on the effects of bright light in healthy subjects is required in order to better understand the effects of bright light therapies. Therefore the aim of this thesis was to shed light on the immediate and circadian effects of bright light exposure on physiological and psychological states of humans. For that purpose we carried out four experiments in which we either varied the type of light we applied (Part I), the timing of exposure (Part II), or the retinal area exposed to the light (Part III). All studies were carried out in several groups of healthy young subjects.

The first question I asked was: Which aspects of light are important to immediately influence and phase-shift human circadian physiology (chapter 2)? To answer this question, I compared bright extraocular light exposure to bright white ocular light exposure during the nighttime in a group of 12 healthy, young subjects under strictly controlled conditions in a time isolation situation. Based on the results of this first experiment, I tried to differentiate the beneficial effects of light on alertness and performance with respect to wavelength by comparing the effects of blue versus red light during the night time in a larger group of subjects (N=80) in a quasi-field setting (chapter3).

Next I asked the question to what extent the timing of ocular light exposure influences the effects on physiological and psychological parameters (chapters 4 and 5). Chapter 4 focuses on the effects of daytime versus nighttime bright light exposure on human psychophysiology, i.e., measurements of subjective sleepiness and alertness together with heart rate, core body temperature, and cortisol. Chapter 5 investigates the effects of daytime versus nighttime bright light exposure on subjective performance measures, such as reaction time, a vigilance task, and the human wake-EEG.

After these explorations of the effects of timing, chapter 6 focuses on the question whether light-induced immediate and phase-shift effects depend on the retinal area that is exposed. In another group of 12 healthy subjects I compared nasal versus temporal retinal bright light exposure during the nighttime and its effects on circadian
physiology. Finally, in chapter 7 I combined three of the datasets on melatonin, subjective sleepiness, and fatigue to compare and correlate them with each other in order to answer the question to what extent suppression of melatonin is a necessary prerequisite for bright light to elicit its activating properties in humans. The thesis concludes with a general discussion (chapter 8) where the findings of the different studies are summarized and discussed.

References


