Light Treatment for Sleep Disorders: Consensus Report.

II. Basic Properties of Circadian Physiology and Sleep Regulation

Derk-Jan Dijk,[1] Ziad Boulos,[2] Charmane I. Eastman,[3]
Alfred J. Lewy,[4] Scott S. Campbell,[5] and Michael Terman[6]

[1]*Institute of Pharmacology, University of Zürich, Winterthurerstrasse 190, CH-8057, Zürich, Switzerland;* [2]*Institute for Circadian Physiology, 1 Alewife Center, Cambridge, MA 02140;* [3]*Biological Rhythms Research Laboratory, Rush-Presbyterian-St. Luke's Medical Center, 1653 West Congress Parkway, Chicago, IL 60612;* [4]*Department of Psychiatry, Oregon Health Sciences University, 3181 S.W. Sam Jackson Park Road, Portland, OR 97201;* [5]*Laboratory of Human Chronobiology, New York Hospital, Cornell University Medical College, 21 Bloomingdale Road, White Plains, NY 10605;* [6]*Department of Psychiatry, Columbia University and New York State Psychiatric Institute, 722 West 168th Street, New York, NY 10032*

Abstract The rationale for the treatment of sleep disorders by scheduled exposure to bright light in seasonal affective disorder, jet lag, shift work, delayed sleep phase syndrome, and the elderly is, in part, based on a conceptual framework developed by nonclinical circadian rhythm researchers working with humans and other species. Some of the behavioral and physiological data that contributed to these concepts are reviewed, and some pitfalls related to their application to bright light treatment of sleep disorders are discussed. In humans and other mammals the daily light-dark (LD) cycle is a major synchronizer responsible for entrainment of circadian rhythms to the 24-h day, and phase response curves (PRCs) to light have been obtained. In humans, phase delays can be induced by light exposure scheduled before the minimum of the endogenous circadian rhythm of core body temperature (CBT), whereas phase advances are induced when light exposure is scheduled after the minimum of CBT. Since in healthy young subjects the minimum of CBT is located approximately 1 to 2 h before the habitual time of awakening, the most sensitive phase of the PRC to light coincides with sleep, and the timing of the monophasic sleep-wake cycle itself is a major determinant of light input to the pacemaker. The effects of light are mediated by the retinohypothalamic tract, and excitatory amino acids play a key role in the transduction of light information to the suprachiasmatic nuclei. LD cycles have direct "masking" effects on many variables, including sleep, which complicates the assessment of endogenous circadian phase and the interpretation of the effects of light treatment on sleep disorders. In some rodents motor activity has been shown to affect circadian phase, but in humans the evidence for such a feedback of activity on the pacemaker is still preliminary. The endogenous

AUTHORS' NOTE: All correspondence should be addressed to Michael Terman, task force chair, and to Derk-Jan Dijk, primary section author.

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circadian pacemaker is a major determinant of sleep propensity and sleep structure; these, however, are also strongly influenced by the prior history of sleep and wakefulness. In healthy young subjects, light exposure schedules that do not curtail sleep but induce moderate shifts of endogenous circadian phase have been shown to influence the timing of sleep and wakefulness without markedly affecting sleep structure.

Key words sleep, circadian rhythms, light, phase response curve, entrainment, sleep homeostasis, nonphotic stimuli, REM sleep, slow-wave sleep, EEG analysis

INTRODUCTION

The light-dark (LD) cycle is a major synchronizer for endogenous circadian rhythms in mammals, including humans. It has long been recognized that in mammals, as in the alga Gonyaulax (Hastings and Sweeney, 1958) and the fruit fly Drosophila melanogaster (Pittendrigh and Bruce, 1957), light is an important synchronizer for endogenous circadian rhythms. As early as 1960, Patricia DeCoursey, working with flying squirrels (Glaucomys volans), demonstrated that a then-unidentified endogenous circadian pacemaker exhibited phase shifts in response to light pulses and, more important, that the effects of these light pulses were dependent on the phase in the circadian cycle at which they were applied, described as a phase response curve (PRC; DeCoursey, 1960). The PRC is a prerequisite for period and phase control, or entrainment, of circadian oscillators whose free running periods deviate from 24 h (Pittendrigh, 1965). According to oscillator theory, which has been successfully applied to biological rhythms research, the phase angle between a 24-h synchronizer (or zeitgeber) and the endogenous oscillator depends on the endogenous period of the oscillator, the shape and amplitude of the phase response curve, and the strength of the zeitgeber (cf., Pittendrigh, 1965). More recent research on laboratory animals has shown that nonphotic stimuli can also be zeitgebers.

Historically, the role of light as a zeitgeber in humans has been controversial and periodic social cues have been postulated also to serve as synchronizers (Aschoff et al., 1971). In a reassessment of effect of daily light presentations, Czeisler et al. (1981) showed that an LD cycle of approximately 150 lux did entrain human circadian rhythms when subjects had no access to auxiliary lighting (as from a bed lamp); however, that experiment did not eliminate the possibility that periodic social contact or the sleep-wake cycle itself (cf. Kronauer et al., 1982) served as zeitgebers. At around the same time, Lewy et al. (1980) demonstrated that bright light (2500 lux) suppresses plasma melatonin in humans, an experiment that has led to numerous investigations on the effects of bright light on human circadian rhythms (e.g., Wever et al., 1983; Wever, 1989; Lewy et al., 1985, 1987; Czeisler et al., 1986, 1989; Broadway et al., 1987; Dijk et al., 1987a, 1989; Eastman, 1987; Honma et al., 1987; Honma and Honma, 1988; Drennan et al., 1989; Rosenthal et al., 1990; Burešová et al., 1991; Campbell and Dawson, 1992; Eastman, 1992; Dawson et al., 1993; Van Cauter et al., 1994). These studies have consistently confirmed that light is the principal zeitgeber in sighted subjects. Outside the controlled laboratory environment, many factors— including the sleep-wake cycle and behaviorally determined exposure to indoor and outdoor light—may combine to determine the perceived LD cycle and thus an individual's pattern of entrainment. In blind subjects, free-running rhythms in various variables including plasma melatonin and sleep propensity have been observed even though these subjects lived in a 24-h social environment and tried to adhere to a 24-h sleep-wake cycle (Miles et al., 1977; Lewy and Newsome, 1983; Sack et al., 1992; Nakagawa, 1992; Klein et al., 1993). The entrainment of some blind subjects may be mediated by residual light input to the suprachiasmatic nuclei (SCN), which can be inferred from the observed suppression of plasma melatonin after exposure to bright light (Czeisler et al., 1995). It remains possible that some blind subjects are entrained by a yet-unidentified "social zeitgeber." Unfortunately, the properties of putative social zeitgebers have not been specified clearly. Taken together, the data demonstrate that light is the major synchronizer of endogenous circadian rhythms in humans.

HUMAN PHASE RESPONSE CURVES FOR LIGHT

It is necessary to quantify the response of the human circadian pacemaker to scheduled exposure to

bright light in order to apply light therapy for sleep disorders. In classical circadian rhythm research, the response to light has been assessed primarily by applying single, brief light pulses to animals that free-ran in constant darkness. This method showed that in both nocturnal and diurnal animals, the phase advance portion of the PRC is located at the end of the subjective night and beginning of the subjective day, that is, at the phase of the circadian cycle that coincides with dawn under entrainment in both nocturnal and diurnal species. Phase delays are induced when light pulses are given at the end of the subjective day and beginning of the subjective night, that is, at the phase of the circadian cycle that coincides with dusk under entrainment.

Application of the PRC protocol to humans is not without problems. In contrast to most small laboratory animals, humans maintain a monophasic sleep-wake cycle, and at certain phases of the circadian cycle, administration of light necessitates a displacement of sleep. However, recent observations suggest that when subjects are kept in very dim light and darkness, sleep displacement does not in itself induce significant circadian phase shifts (Kronauer et al., 1993a). It is difficult to maintain human subjects in constant darkness. Therefore, unlike with animals, the human PRC must be generated against a background of low-intensity light, which has been shown to modulate the response to bright light (Czeisler et al., 1989). Since subjects close their eyes during sleep, or turn off the light when they go to bed, the sleep-wake cycle generates an LD cycle that may also affect the observed response (Beersma et al., 1987; Eastman, 1990). In humans the sleep-wake cycle is only loosely coupled to the circadian pacemaker and does not serve accurately as phase marker of the circadian pacemaker. Thus phase shifts have to be assessed by other variables, such as core body temperature (CBT; e.g., Wever, 1979) and melatonin secretory activity (e.g., Lewy et al., 1985; Shanahan and Czeisler, 1991). As an experimental strategy, some members of the task force point to the advantage of measuring multiple circadian endpoints in order to clarify the response of the pacemaker to phase-shifting interventions; other members, however, feel that proper measurement of a single variable—for example, melatonin under dim light conditions or CBT under demasked conditions (see below)—is ordinarily adequate.

Despite these problems, human PRCs have been derived using light pulses administered over 3 consecutive days (Czeisler et al., 1989) as well as on a single day (following the animal model; Minors et al., 1991). In the single pulse experiment, the duration of the 5,000-lux light pulse was 3 h, whereas in the triple-pulse experiment, the duration of a 10,000-lux pulse was 5 h. In either case, phase delays were obtained when light exposure was centered 1 to 3 h before the minimum of the endogenous component of the CBT rhythm, which under entrained conditions in healthy young subjects is located approximately 1 to 2 h before the habitual time of awakening (Czeisler et al., 1992; Kräuchi and Wirz-Justice, 1994; Van Cauter et al., 1994). Phase advances were obtained when light was centered 1 to 4 h after the CBT minimum. In both PRCs there were no phase shifts when light was applied during the major part of the subjective day. With light presented close to the CBT minimum, the triple-pulse procedure can produce phase shifts of up to 12 h (see also Eastman, 1992), while the single-pulse procedure produces smaller shifts. Although some members of the task force find this contrast suggestive of different underlying mechanisms, others find it unremarkable given that the phase shift is assessed at different intervals following the stimulus. An important characteristic of both PRCs is that the largest phase shifts are obtained when light coincides with the nocturnal sleep phase under entrainment. This may explain why in some protocols in which sleep was not displaced, or subjects were not awakened for light exposure, little or no phase delay was obtained (Honma et al., 1987; see, however, Honma and Honma, 1988).

Kronauer (1990) developed a mathematical model to account for the three-pulse PRC data. According to this model, a single light pulse centered around the minimum of the CBT rhythm serves to reduce the amplitude of the oscillator even though it does not affect circadian phase. Such amplitude reduction renders the pacemaker more sensitive to subsequent light pulses, which then can induce large phase shifts, that is, type 0-like resetting (Kronauer and Czeisler, 1993; Jewett et al., 1994). The predicted reduction of amplitude after one or two light pulses centered at the CBT minimum was subsequently demonstrated experimentally (Jewett et al., 1991; Minors et al., 1991). Thus, in addition to phase, amplitude is an important parameter of the human circadian system. The Kronauer model can predict phase and amplitude changes even when the LD schedule is complex, and may thus be relevant to clinical applications in situations where daily light exposure cannot be reduced

to a pattern of discrete bright light pulses, but also includes extended, dimly lit intervals and a distribution of light exposure modified by sleep (cf. Czeisler et al., 1990; Eastman, 1990).

Recently, Beersma and Daan (1993) have argued that the observed changes in amplitude may not reflect pacemaker amplitude but rather changes in oscillatory processes downstream from the central pacemaker. Further, they argued that type 0-like resetting as observed in the three-pulse PRC could be produced cumulatively by three type 1 resets. Kronauer et al. (1993b) replied that some of the assumptions used in Beersma and Daan's solution are incompatible with a pacemaker that can exhibit only type 1 resetting (see also Strogatz, 1990). Laking-Thomas (1993) has pointed out that a pacemaker that exhibits changes in phase and amplitude, and can therefore show type 0 resetting, has the advantage of parsimony for a model that can be applied to many organisms. An important consideration in these discussions is that although the observed variable—for example, CBT—may exhibit changes in amplitude as well as type 0 resetting, it cannot be concluded that the central nervous pacemaker itself is a complex oscillator with at least two-state variables. However, as long as the central pacemaker cannot be accessed directly, this consideration remains speculative.

NEUROANATOMICAL PATHWAYS MEDIATING THE EFFECTS OF LIGHT ON CIRCADIAN RHYTHMS

The evidence is overwhelming that in mammals the SCN of the hypothalamus are the loci of the endogenous circadian pacemaker (Meijer and Rietveld, 1989; Klein et al., 1991), as confirmed by the demonstration that a key parameter of the circadian system—the intrinsic period, τ—can be transferred to a host animal with an SCN lesion by transplantation of fetal SCN tissue (Ralph et al., 1990). The human SCN has been described in detail (Mai et al., 1991), and anatomical changes in the SCN have been documented in relation to gender and aging (Swaab et al., 1988). In addition, case studies have been reported in which lesions of the SCN resulted in severe disruption of the sleep-wake cycle (for review, see Cohen and Albers, 1991).

In the intact animal, light information reaches the SCN via the retinohypothalamic tract (RHT), a monosynaptic pathway from retinal ganglion cells to the SCN, which has also been demonstrated in humans (Sadun et al., 1984), and via a second pathway (the geniculate-hypothalamic tract, GHT) via the intergeniculate leaflet of the geniculate nucleus. Light pulses induce long-lasting increments or decrements in firing rates of specialized neurons in the SCN (Groos and Meijer, 1985). Furthermore, light pulses have been shown to increase the expression of the immediate early gene c-fos, and other immediate early genes, in a phase- and dose-dependent manner (Rusak et al., 1990; Kornhauser et al., 1990; Sutin and Kilduff, 1992; see also Ginty et al., 1993). Surprisingly, no consensus has been reached over which neurotransmitter system is primarily involved in transducing light information to the SCN. Early findings indicated that acetylcholine (Earnest and Turek, 1985, Colwell et al., 1993) and γ-amino butyric acid (GABA; Ralph and Menaker, 1985, 1986) were key factors in transducing information via the RHT, and more recent evidence points to a critical role for excitatory amino acids (Meijer et al., 1988; Colwell et al., 1991; Abe et al., 1991; Vindlacheruvu et al., 1992; Rea et al., 1993; Ding et al., 1994) in conjunction with GABA (Moore and Speh, 1993). Neuropeptide Y is generally believed to be the neurotransmitter of the GHT (for reviews, see Meijer and Rietveld, 1989, and Morin, 1994).

Wavelength and light intensity response curves have been generated for the phase-shifting effects of light in rodents (Takahashi et al., 1984; Nelson and Takahashi, 1991). The spectral sensitivity curve for light-induced phase shifts in hamsters shows a single peak at 500 nm, suggesting the involvement of rods, whereas the involvement of cones is suggested by the intensity response curve given that the threshold for inducing phase shifts is rather high (Takahashi et al., 1984). Some evidence for species differences has been obtained (Joshi and Chandrashekaran, 1985; Meijer et al., 1989; Hotz et al., 1990), and it also has been suggested that the effects of light on the circadian pacemaker are mediated via a yet-unidentified photoreceptor (Foster et al., 1991).

For humans, intensity, pulse duration, and wavelength response curves for phase shifts of the circadian system are not yet available or are incomplete. Recent data indicate that the light intensity needed to affect the pacemaker is lower than originally thought. Exposure to 1 h of light at 500 lux has been reported to shift the melatonin rhythm (Laakso et al., 1993), and melatonin suppression has been observed with as little as 250 lux (McIntyre et al., 1989). Repetitive exposure to 5-h light pulses at 1250 lux has been successful in

shifting the CBT rhythm (Boivin et al., 1994). Such sensitivity to light is consistent with entrainment to ordinary room light under laboratory conditions (e.g., Czeisler et al., 1981; Wever, 1989) and may explain why entrainment persists in the natural living environment even when daily exposure to bright light is quite limited (Savides et al., 1986; Campbell et al., 1988).

MASKING EFFECTS OF LIGHT

The LD cycle has a direct "masking" effect on many variables, including sleep. Aschoff has distinguished between two different effects of a zeitgeber on rhythmic processes: "It entrains the rhythm by controlling the phase of the pacemaker's oscillation, and it may influence the variable measured (the overt rhythm) in a more direct way, with or without a relationship to the process of entrainment" (Aschoff et al., 1982, p 16). The distinction is of special importance in the present context because many variables that are used as markers of the circadian pacemaker are also subject to masking by light. For instance, plasma melatonin, which is considered a reliable marker of the circadian system, and for which there is good documentation of the neuroanatomical pathway by which the pacemaker generates the overt rhythm (Moore and Klein 1974), can be suppressed by light exposure of sufficient intensity (Lewy et al., 1980; McIntyre et al., 1989). As a consequence, melatonin cannot be used as a phase marker when measured during a treatment with bright light. Similar arguments apply to CBT, which can be readily driven upward by exposure to bright light (Badia et al., 1990; Dijk et al., 1991b; Cajochen et al., 1992; Bunnell et al., 1992)—an effect that may be mediated by the light-induced suppression of melatonin (Strassman et al., 1991; Cagnacci et al., 1992). Sleep itself is subject to masking effects by light. In the rat, the amount of REM sleep is enhanced during schedules with continuous or intermittent light (Borbély, 1980). In the squirrel monkey, masking effects of an LD cycle have been described for brain temperature and sleep propensity even given an SCN lesion (Edgar, 1986). Although it is not known by which neuroanatomical pathways these effects of light are mediated, there is growing evidence that several hypothalamic areas other than the SCN are innervated by direct or indirect retinal projections that are not part of the primary visual system (Card and Moore, 1991). Such findings point to the involvement of noncircadian mechanisms in the effects of light treatment (see related task force section, Campbell et al., 1995 [this issue]; Wirz-Justice et al., 1993) and make it important to develop and apply experimental designs that distinguish between circadian and noncircadian effects.

ASSESSMENT OF CIRCADIAN PHASE, AMPLITUDE, AND WAVEFORM

To investigate whether a bright light therapy has affected circadian parameters, adequate assessment of these parameters is of critical importance. The most widely used marker has been the circadian rhythm of CBT, which is vulnerable, however, to masking effects of the rest-activity and sleep-wake cycles and associated changes in posture and light exposure (cf. Kleitman and Doktorsky, 1933; Barret et al., 1993). An alternative view, expressed by a minority of the task force, is that the circadian component of the rhythm is revealed during sleep, and daytime increments in CBT are primarily the result of physical activity during waking hours. Other factors that affect CBT include menstrual cycle phase (Lee, 1988), extremes of ambient temperature (e.g., Kreider and Iampietro, 1959), and alcohol ingestion (Eastman et al., 1994b).

The clinical use of CBT measures outside the confines of laboratory controls on masking is therefore problematic. The nocturnal CBT minimum (T_{min}) has served usefully as a circadian phase marker when sleep occurs at a normal time, but in situations where sleep is displaced—for example, shift work or sleep phase disorders (see related task force sections, this issue, Eastman et al., 1995; Terman et al., 1995)—the signal is obscured. If sleep and the associated changes in posture and light exposure produce a masking effect, as has been posited, the endogenous circadian phase of T_{min} could be elucidated by studying subjects under constant behavioral and environmental conditions that are maintained throughout at least one circadian cycle. The constant routine protocol (Mills et al., 1978; Czeisler et al., 1985) provides such a control by eliminating or distributing masking effects of sleep, meals, posture, and so on, over the 24-h day, under exposure to constant levels of low-intensity light (< 150 lux), which does, however, eliminate the normal daily dark interval. This procedure affords direct assessment of circadian phase, amplitude, and waveform (Brown and Czeisler, 1992) and has proved a valuable tool for analysis of sleep disorders (Morris

et al., 1990). Some caution in the interpretation of the results is needed because constant routines usually last longer than 24 h and thereby introduce sleep deprivation as a potential confounding factor.

Beyond experimental manipulations of the subject and environment, masking effects of sleep and activity on CBT can be partialed out mathematically (e.g., Folkard et al., 1991). This "demasking" method has most often been applied to CBT measurements averaged over several weeks under steady-state conditions, in which case short-term phase shifts cannot be assessed. Additionally, demasking procedures recently have been applied to track daily trends during phase shifts (Eastman et al., 1992, 1994a; Minors et al., 1994a). Different methods have added constants to the CBT data to correct for masking influences of sleep alone or sleep and wake-time activity, such constants based on normative data or adjusted to individual temperature curves. The validity of demasking for revealing underlying pacemaker properties has been questioned given that (a) the masking effect of sleep on CBT may not be independent of circadian phase (Wever, 1985), (b) it is modulated by the duration of wakefulness preceding sleep (Minors et al., 1994b), and (c) there are interindividual differences in masking effects of sleep on CBT (Wever, 1985). These complications are overlooked by most demasking algorithms, and further research would be useful for comparing phase estimates with those obtained, for example, by melatonin sampling or for CBT under the constant routine. The task force concurs, however, that demasking methods may provide a practical tool for field studies.

CIRCADIAN EFFECTS OF NONPHOTIC STIMULI

Recent observations that nonphotic, arousing stimuli, such as access to a novel running wheel or the administration of triazolam, induce hyperactivity in rodents and thereby influence the phase and period of their circadian rhythms have uncovered previously unsuspected feedback effects of behavior on circadian pacemakers (Mrosovsky and Salmon, 1987; Van Reeth and Turek, 1989; Edgar et al., 1991). Some of these effects appear to be mediated by the prominent serotonergic projection from the dorsal raphé and the NPY-containing projection from the IGL to the SCN (Biello et al., 1991; Cutrera et al., 1994). In humans, the evidence for such feedback of activity, arousal, or the sleep-wake cycle on the endogenous circadian pacemaker is scarce and equivocal (Kronauer et al., 1993a; Van Reeth et al., 1994).

Animal studies (Cassone et al., 1986; Armstrong, 1989), as well as recent human studies (Lewy et al., 1992), have demonstrated that melatonin can induce phase shifts of overt rhythmicity. In humans, appropriately timed exogenous administration of the hormone has been shown to alleviate jet lag, stabilize sleep onset, and, in blind subjects, induce phase shifts in the free-running rhythm of melatonin (Arendt et al., 1986; Folkard et al., 1990; Sack et al., 1991). However, entrainment of free-running circadian rhythms by exogenous melatonin has not yet been conclusively demonstrated. Melatonin receptors and binding sites have been identified in the rodent and human SCN (Vaněček, 1987; Reppert et al., 1988). In the rat, melatonin receptor density is affected by light conditions (Gauer et al., 1992). The circadian rhythm of discharge rate of the SCN can be reset by melatonin in vitro (McArthur et al., 1991), and melatonin induces expression of the immediate early gene c-fos (Kilduff et al., 1992). Since in mammals the rhythm of melatonin is driven by the SCN, it has been suggested that melatonin provides a feedback to the SCN, which conceivably could stabilize entrainment.

FACTORS AFFECTING LIGHT INPUT TO THE CIRCADIAN PACEMAKER

The monophasic sleep-wake cycle of humans and the factor of sleep in darkened rooms creates another source of feedback in that the perceived LD cycle is influenced by these behavioral factors. Thus, even though light can affect the human circadian pacemaker directly (and phase shifts can be induced even when the sleep-wake cycle is fixed), variations in the sleep-wake pattern under free-running conditions and outside the laboratory are a major determinant of light exposure. Such feedback may be responsible for a phenomenon called "phase trapping," that is, periodic modulation of the phase relation between the sleep-wake cycle and the CBT rhythm, as has been observed in free-running studies (Kronauer et al., 1982; Beersma et al., 1987). It may also be responsible for the classical observation that in humans who free-run while self-selecting their LD cycle, τ is close to 25 h, whereas protocols that eliminate or control this influence show τs closer to 24 h (Klerman et al., 1992; Sack et al., 1992; Campbell et al., 1993). Feedback of the

LD cycle created by the sleep-wake cycle may play a role in delayed sleep phase syndrome, for example, and may affect the efficacy of light therapy (see related task force section, Terman et al., 1995). If the sleep episode is located late in the circadian cycle of light sensitivity, sleep will prevent light from reaching the pacemaker. During light therapy, sleep might be displaced and the circadian cycle of light sensitivity advanced relative to clock time; upon termination of the light therapy, sleep might recapture its normal phase relation with the circadian cycle of light sensitivity, and environmental light might again fail to reach the pacemaker at its sensitive phase. As a result, the pacemaker could drift to later hours.

Retinal factors per se have been hypothesized to modulate light input, thus potentially shaping the internal representation of the zeitgeber. It has been demonstrated that retinal sensitivity exhibits a circadian variation both in rats and humans (for review, see Remé et al., 1991). There is growing evidence that a circadian rhythm of visual sensitivity persists after SCN lesions in the rat (Terman and Terman, 1985; Terman et al., 1993). Such circadian variation, whether generated by a yet-unspecified efferent pathway or by a local retinal oscillator, might constitute a mechanism that influences the phase of entrainment in interaction with external light levels.

INTERACTION BETWEEN THE CIRCADIAN AND HOMEOSTATIC REGULATION OF SLEEP: IMPLICATIONS FOR THE DESIGN AND INTERPRETATION OF BRIGHT LIGHT STUDIES

The endogenous circadian pacemaker is a major determinant of sleep propensity, sleep timing, sleep structure, and the consolidation of sleep and wakefulness. Adjustment of circadian phase or amplitude by light treatment can be expected to induce changes in these parameters. The circadian variation of sleep propensity exhibits a maximum at the trough of the circadian rhythm of CBT and sleep duration is longest when sleep episodes are initiated shortly after the maximum of CBT (Czeisler et al., 1980; Zulley et al., 1981; Dijk and Czeisler, 1994). Sleep episodes initiated on the later part of the rising limb of the CBT rhythm are disrupted and of short duration. REM sleep reaches its maximum shortly after the time of T_{min}. The deep stages of non-REM sleep—that is, stages 3-4 or slow wave sleep (SWS) during the major sleep episode—appear to be little affected by the circadian pacemaker (Hume and Mills, 1977; Weitzman et al., 1980; Campbell and Zulley, 1989; Campbell et al., 1995). Sleep spindle activity in non-REM sleep is markedly affected by endogenous circadian phase (Dijk and Czeisler, 1995).

The prior history of sleep and wakefulness is another determinant of sleep propensity and sleep structure (Webb and Agnew 1971a, 1971b; Borbély et al., 1981; Dijk and Czeisler, 1994). Thus SWS and computer-detected slow-wave activity (SWA) in the electroencephalogram (EEG) decrease in the course of sleep independent of circadian phase (Åkerstedt and Gillberg, 1981; Dijk et al., 1990a, 1990b, 1991a; Dijk and Czeisler, 1995) and an extension of wakefulness results in an enhancement of SWS and SWA in subsequent sleep (Webb and Agnew 1971a; Borbély et al., 1981). Even REM sleep, which is generally thought to be primarily under circadian control, is affected by the prior history of sleep and wakefulness. After total sleep deprivation, an REM rebound has been observed in the second recovery night (Williams et al., 1964). Furthermore, the observed increase of REM sleep duration in the course of the nocturnal sleep episode is in part due to a sleep-dependent disinhibition of REM sleep (Dijk and Czeisler, 1995). Likewise, the latency to REM sleep can be reduced by reducing the pressure for non-REM sleep (Campbell, 1987; Feinberg et al., 1992).

The process tracking the prior history of sleep and wakefulness is not located in the SCN, since sleep deprivation in animals with SCN lesions still results in compensatory responses (Tobler et al., 1983; Mistlberger et al., 1983; Trachsel et al., 1992). Observed sleep-wake patterns result from an interaction between the output of the endogenous circadian pacemaker and the regulatory processes that subserve sleep homeostasis (Webb and Agnew 1971b; Borbély, 1982; Daan et al., 1984; Beersma et al., 1987; Edgar et al., 1993). A quantitative analysis of this interaction has demonstrated that sleep consolidation and sleep structure are dependent on an appropriate phase relation between the sleep-wake cycle and the endogenous circadian pacemaker (Dijk and Czeisler, 1994, 1995). The neuroanatomical locus of and the neurophysiological processes involved in this interaction between the output of the pacemaker and sleep homeostasis are not known (Watts, 1991).

The interaction between circadian and homeostatic regulation of sleep complicates the interpretation of

observed changes in sleep parameters during and after bright light treatment if during treatment sleep is displaced or curtailed. Sleep displacement or curtailment may be necessary in order to be able to expose subjects to bright light at a circadian phase, which normally is shielded from light input by sleep. Observed changes in sleep parameters such as SWS, sleep latency, or subjective alertness, which are very sensitive to prior sleep loss and the duration of prior wakefulness (Carskadon and Dement, 1979; Borbély et al., 1989; Dijk et al., 1987b, 1990a; Brunner et al., 1990), may not be due to bright light induced changes in phase or amplitude of the circadian system, but rather may be related to sleep loss during the treatment. Conversely, inadequate EEG analysis may result in failure to detect treatment-induced changes in the EEG. Adequate control procedures, polysomnographic recording of sleep during the treatment period, and quantitative EEG analysis (Borbély, 1990) may help avoid misinterpretation of the data. Effects of bright light exposure and the associated phase shift of the circadian system on polysomnographically determined sleep duration and sleep structure have been investigated in healthy young subjects (Dijk et al., 1987a, 1989; Drennan et al., 1989; Campbell and Dawson, 1992). A consistent finding in these studies is that the shifts in the circadian system as indexed by CBT or melatonin are associated with shifts in the timing of the sleep propensity rhythm. Thus sleep initiation and termination are affected, whereas sleep structure is not markedly affected.

CONCLUSION

Remarkable progress has been made in the understanding of the neuroanatomical structures and neurophysiological processes underlying circadian rhythmicity. The empirical findings and theoretical concepts are transparent, and their applications provide powerful tools in the study and treatment of circadian disorders. The rigorous application of these concepts to the study of sleep disorders related to circadian rhythm abnormalities has until now been limited. Strict experimental designs and quantitative models, in which all of the processes involved in the timing of sleep are taken into account, will aid in the development of new—and the understanding of existing—effective bright light treatments for sleep disorders related to the circadian system.

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