Chronobiology of Sleep in Children

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A circadian rhythm is defined as an intrinsic biologic rhythm with a periodicity (peak-to-peak duration) of approximately 24 hours. Circadian rhythms are a basic property of higher life forms, including plants and animals. In mammals, circadian rhythms are coupled to the timing of sleep and wakefulness. Circadian rhythms undergo a developmental course, from their beginnings in utero to adult expression. This chapter describes basic properties of circadian rhythms and then reviews some of their fundamental properties as they develop during childhood. Animal studies are employed to illustrate findings that are applicable to infants and children.

Entrainment of the fetus to day and night begins in utero as a passive response to maternal melatonin secretion. In the perinatal period, various expressions of an endogenous circadian pacemaker neuroanatomic structure (including the suprachiasmatic nucleus, the pineal body, and their connections to the retina) develop sequentially, resulting in the successive appearance of circadian rhythms of melatonin secretion, temperature, wakefulness, and sleep. Circadian rhythms are fully expressed within the first 6 months of life.

In the infant and young child, the timing of light exposure controls the timing of melatonin secretion and consequently the timing of sleep. In early childhood and in preadolescent children, the phase relationship of the child's circadian rhythm to environmental light and darkness is variable. The hour at which the child is awakened, the timing and brightness of artificial lighting after sunset and before sunrise, the timing of exercise, the child's feeding schedule, and the timing of social interactions might each influence the child's timing of sleep propensity. The number of hours of darkness (less than 3 lux) to which the child is exposed may influence the duration of the child's melatonin secretion and the number of hours that the child sleeps.

It is becoming increasingly clear that sleep quality impacts human development. Both the hours at which a child sleeps and the duration of sleep appear to be modifiable. Beginning in utero, and continuing through childhood, environmental and social activities are capable of influencing the timing and duration of sleep.

THE CIRCADIAN RHYTHM SYSTEM: BASIC PROPERTIES

The duration of daylight changes continually. The magnitude of change from the shortest to the longest day of the year is directly dependent on latitude. The farther one is from the equator, the greater the change from shortest day to longest day. Without artificial light, human and mammalian ancestors were in synchrony with changes in photoperiod (day length) that varied from greater than to less than 12 hours. The circadian rhythm system must be viewed as having the capacity to track continually changing times of light exposure, including changing times of sunrise and of sunset.

In contrast to sleep homeostasis, in which sleep drive increases with increased awake time, the body's internal clock mechanism, or circadian rhythm, exhibits a cyclical tendency that is mostly independent of prior wakefulness—this is the circadian rhythm of sleep propensity.[1] Thus, a child or adolescent may be unable to begin nocturnal sleep at a desired hour despite sleeping little on previous weekday nights and exhibiting daytime sleepiness during school hours. For example, a child with a 9 PM bedtime might remain awake until midnight. Biologic markers of circadian rhythms, such as the daily rise and fall in core body temperature, continue in the absence of normal social, lighting, or other time cues. Each individual possesses a precise internal clock, the periodicity of which

can be "unmasked" in various types of laboratory protocols. This clock typically has a peak-to-peak cycle duration of approximately 24.1 to 24.3 hours.[2,3]

Period Length

The duration of the circadian rhythm (Fig. 8–1), sometimes referred to as period length, or tau, appears to be a genetically heritable property of the suprachiasmatic nucleus (SCN). Period length (see Fig. 8–1A) is measured from one cycle's temperature minimum to the next, or from the onset of melatonin secretion on consecutive days, in experimental conditions that eliminate environmental influences.[4] The SCN contains an autonomous circadian pacemaker. It is the site of generation of circadian rhythmicity. Metabolic and electrical activity rhythms in the SCN have been observed in vivo, and the SCN maintains rhythmicity in vitro. A transplanted SCN from a donor can restore circadian function after the destruction of a host's SCN. Single SCN "clock cells" exhibit independent firing-rate rhythms. The proteins responsible for rhythmicity within the SCN have been identified in circadian mutants (tau mutant hamsters and Clock mutant mice). These mutants have enabled the isolation of so-called clock genes.[5]

Amplitude

The amplitude of the circadian rhythm—that is, the change in a measured parameter from nadir to peak (acrophase)—is an estimate of the biologic capacity to oscillate every day from deep sleep to intense alertness. The amplitude of the circadian rhythm appears to be minimal at birth and to attain adult levels within the first year of life, as measured by melatonin or temperature. Figure 8–1B shows the effects of constant routine (such as staying in bed under conditions of continuous dim illumination for 24 hours) on damping circadian rhythm amplitude. Factors such as exercise and a constant bed and wake-up time do not affect the amplitude of the circadian rhythm.[6]

Phase

The phase of a circadian rhythm refers to the relationship between the internal timekeeping mechanism and the environmental time. Ideally, core temperature drops and sleepiness occurs at the desired hour of sleep, and body temperature is rising and an individual feels rested at the desired hour of awakening. This is referred to as being "in phase." Phase advance refers to the internal clock's being set early with respect to environmental time, and phase delay refers to the internal clock's being set late with respect to environmental time (Fig. 8–1C). The tendency for

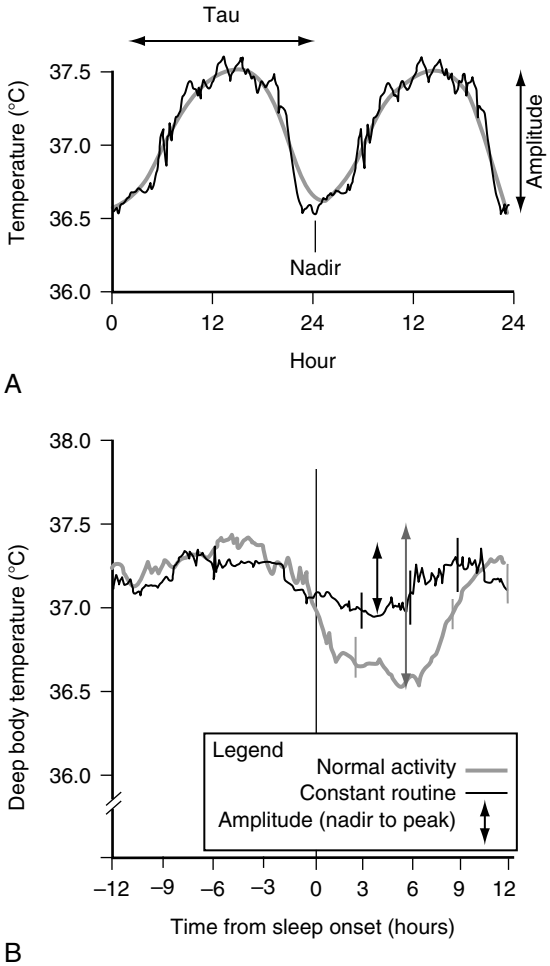
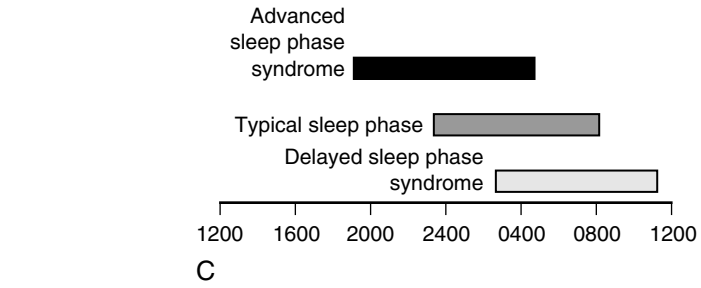


Figure 8–1. Properties of a single cycle of the circadian rhythm. **A,** One cycle of the circadian rhythm of temperature drawn twice to illustrate the duration of the circadian rhythm (tau, or τ), here measured from succeeding temperature nadirs, and the amplitude of the circadian rhythm, in this case, temperature difference from apogee to nadir. **B,** The amplitude of the circadian rhythm is reduced by the subject remaining in bed for 24 hours (constant routine, CR) compared to the amplitude of temperature from peak to nadir when the subject is engaged in normal waking activity.



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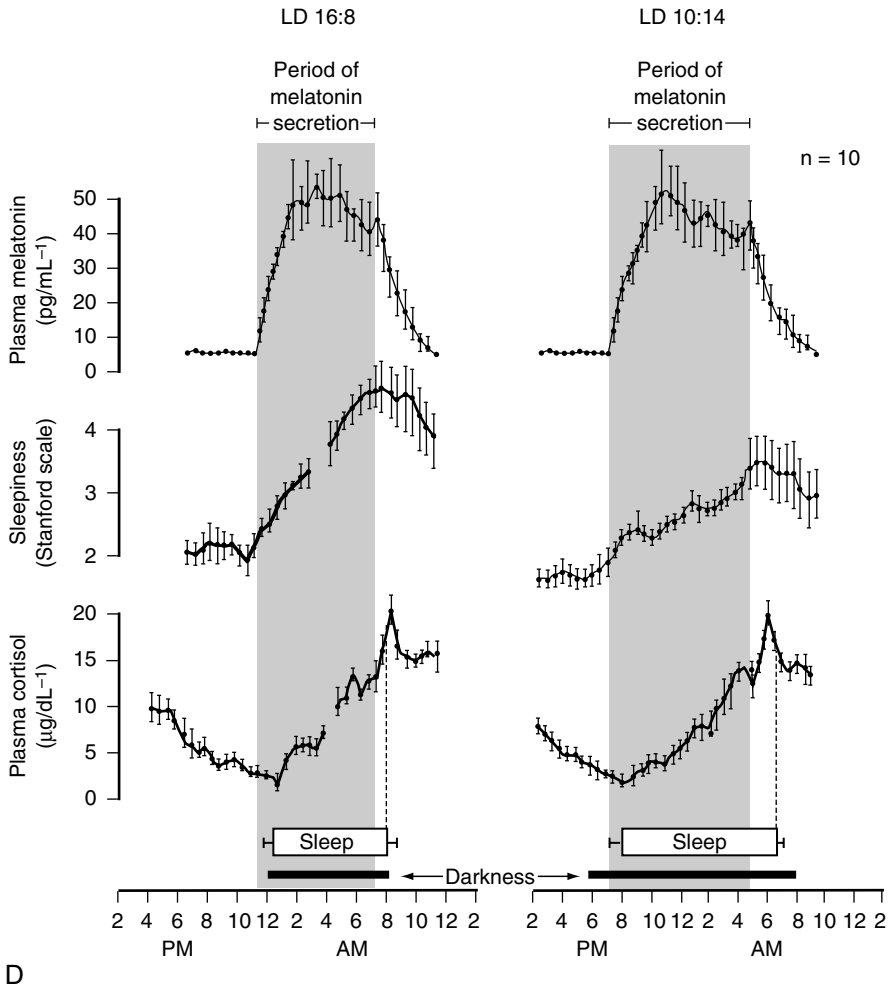

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Figure 8–1. cont'd—C, Phase of circadian rhythm refers to the relationship of the internal clock to environmental timing of light and dark, the *top bar* illustrates advanced sleep-phase syndrome (sleep from 7:00 PM to 5:00 AM), the *middle bar* illustrates normal phase timing (sleep from 11:00 PM to 8:00 AM), and the *bottom bar* illustrates delayed sleep phase syndrome (sleep from 2:30 AM to 11:00 AM). **D,** The relative duration of biological day to biological night changes as the light-to-dark ratio is changed from 16 hours of light and 8 hours of darkness *(left, black bar)* to 10 hours of light and 14 hours of darkness *(right, black bar),* resulting in an increased duration of melatonin secretion *(top),* delayed cortisol secretion *(middle),* and increased duration of temperature suppression *(bottom).* (A and C, redrawn from Baker SK, Zee PC: Circadian disorders of the sleep wake cycle. In Kryger M, Roth T, Dement W (eds): Principles and Practice of Sleep Medicine, 3rd ed. Philadelphia, WB Saunders, 2000, pp 607, 610; D redrawn from Wehr TA, Aeschbach D, Duncan WC: Evidence for a biological dawn and dusk in the human circadian timing system. J Physiol 2001;535:937-951.)

phase to be delayed appears to increase from childhood to adolescence.[7]

Morningness–Eveningness Preference and Phase

The duration of an individual's circadian rhythm is correlated with "owl" versus "lark" behavior (referred to as morningness versus eveningness): the longer the period length, the greater the owl tendencies. Evening types (owls) have a later onset of melatonin secretion, their morning temperature rise is later, and they wake up later than do morning types. Dropping temperature is related to sleep onset and rising temperature is correlated with preferred wake-up time.[8] Individuals who are maximally alert in the morning have an earlier peak in circadian temperature than do individuals who are most alert in the evening. Individuals with morning preference have a greater change in temperature from nadir to peak. These lark types awaken and begin sleep earlier than individuals with evening preference.[9] The phase of temperature and melatonin secretion can be predicted fairly accurately by having an individual maintain a sleep log for several weeks, even with irregular sleep times.[10] With the approach of adolescence, circadian phase shifts to a later hour, as does an increase in evening preference for activities. This occurs at about age 12 to 13 years.[11]

Biological Day and Biological Night

A property of any waveform is the proportion of the wave cycle during which values are above the mean as opposed to below the mean. From the perspective of circadian rhythms, this

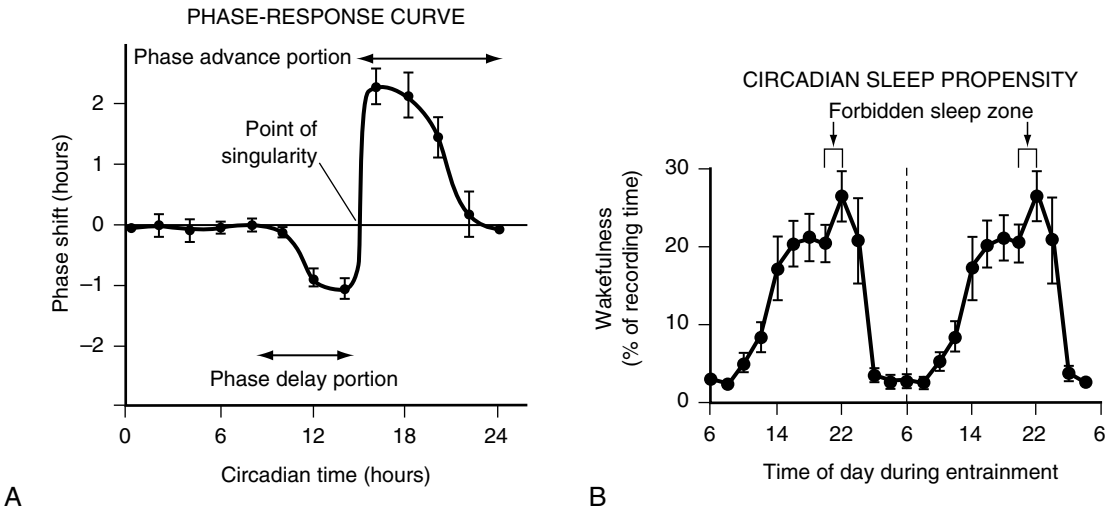

Figure 8–2. A, The phase-response curve to light (in Syrian hamsters) showing the change in the phase of the circadian rhythm in response to exposure to light at different times. The phase-response curve shows no phase-shifting effect of light during the circadian hours of normal light exposure (typically, the hours of daylight). Exposure to light *before* the moment of singularity results in a maximal phase-delaying effect during the hours of normal darkness (negative numbers). Exposure to light *after* the moment of singularity results in a maximal phase-advancing effect during the hours of normal darkness (positive numbers). A person's circadian time must be known to predict whether the response to bright light will have a phase-advancing or a phase-delaying effect. Point of singularity: the time at which light exposure (or another zeitgeber) switches from having a phase-advancing to a phase-delaying effect on the circadian rhythm. **B,** Circadian sleep propensity double-plotted for one circadian cycle, showing the forbidden sleep zone (a brief time period typically preceding sleep onset), during which sleep is least likely to occur during the circadian day. (A, redrawn from Takahashi JS, Zatz M: Regulation of circadian rhythmicity. Science 1998;2178:1104-1111; B, redrawn from Dijk D-J, Czeisler CA: Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves and sleep spindle activity in humans. J Neurosci 1995;15:3526-3538.)

refers to the ratio of biological day (above the mean) to biological night (below the mean). Figure 8–1D displays two different lengths of environmental light and dark: a 16-hour light period followed by an 8-hour dark period (on the left) and a 10-hour light period followed by 14 hours of darkness (on the right). At latitudes both north and south of the equator, half the year has day length greater than night length. This means that environmental night is greater than 12 hours for half of the year in almost every country, a situation that was far more behaviorally significant before the invention of indoor light, beginning with candles. Figure 8–1D shows that the duration of biological night can change in response to changing durations of environmental night length, including a lengthening in the duration of melatonin secretion.[12]

The capacity to increase the duration of biological night is a critical factor in appreciating the flexibility of the human sleep–wake cycle. Contemporary humans, in essence, attempt to exist year round on a schedule similar to a short summer night.[13]

Implicit in the description of long versus short biological nights is the hypothesis that there is one switch (entrained to dusk) for the beginning of biological night, and a second switch (entrained to dawn) for the beginning of biological day (Fig. 8–3).[13] The end of biological night does not occur at a set time after its beginning, and the time of awakening is not a constant interval after dim-light melatonin onset (DLMO). Instead, the switches for biological night and day are capable of tracking changing environmental day lengths.[9] This is referred to as a two-oscillator model.[14] The duration of sleep, temperature suppression, and cortisol suppression each increases as biological nights lengthen. The concept of a flexible (within limits) biological night has significant implications for human development.

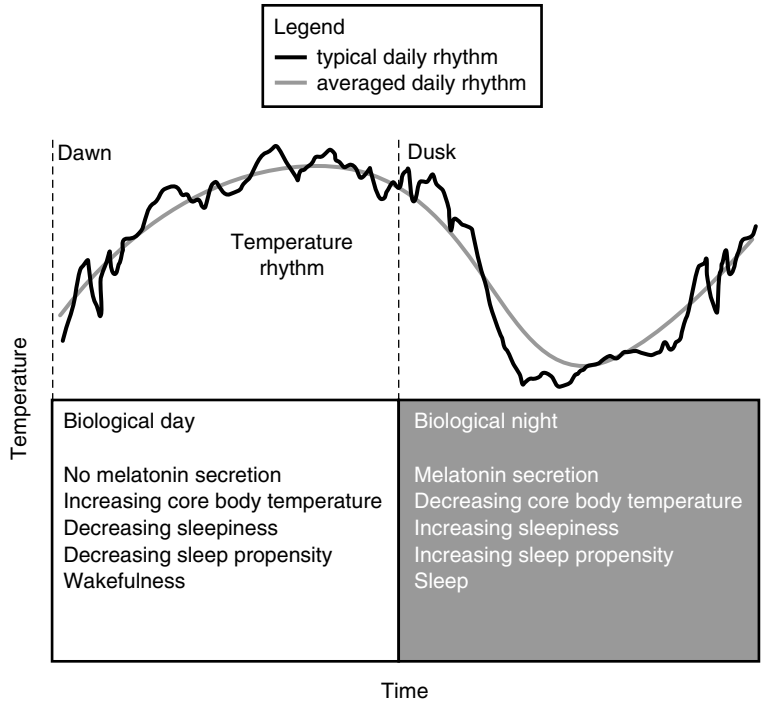

Figure 8–3. Biological day coincides with the environmental time from dawn to dusk, and in diurnal species, including humans, it exhibits qualities compatible with alertness and activity. In diurnal species, biological night, which coincides with darkness, is compatible with rest and immobility. The durations of biological day and biological night are responsive to changes in the duration of daylight as it varies from less than 12 to greater than 12 hours, depending on latitude and season. (Redrawn from Wehr TA, Aeschbach D, Duncan WC: Evidence for a biological dawn and dusk in the human circadian timing system. J Physiol 2001;535:937-951.)

Consolidated Sleep Period

Optimal sleep is one manifestation of biological night. The timing of biological night and an increased sleep propensity (sleepiness) are initiated by the beginning of darkness, or dusk, which is signaled from the retina to the SCN via the retinal hypothalamic pathway (Fig. 8–4). Dusk permits the expression of melatonin (i.e., DLMO) by the pineal body, and it begins the nocturnal phase of the circadian rhythm, or biological night. This includes a drop in core body temperature, which reaches a nadir approximately 2 hours prior to habitual wake-up time (see Figs. 8–1A and Fig. 8–3), and a concomitant decrease in glucose utilization,[15] urinary metabolism, and appetite. After the temperature begins its nightly drop and serum melatonin begins its rise, sleep propensity increases rapidly and the consolidated period of nocturnal sleep begins (see Fig 8–3).[16]

Rate of Change from Biological Day to Biological Night

Human circadian rhythms have traditionally been represented graphically as a plot of core body temperature or melatonin secretory levels averaged from several subjects. The resulting plot of mean values resembles a sine wave (Figs. 8–3 and 8–5A) that is similar to a frequency histogram recording electrophysiologically from SCN neurons.[17] However, if melatonin secretory profiles are measured consecutively, time-locked to melatonin onset or offset, the resulting waveform resembles more of a square wave, with a rapid transition from biological day to biological night, as shown in Figure 8–5B.[8] This rapid transition is consistent with experimental findings in constant-routine protocols of a brief sleep "gate," before which sleep is unlikely to occur and after which sleep is likely to occur.[18] As day changes to night, the output of the SCN switches an organism from one mode of functioning, in which it is interactive with its environment, to another, in which it is nonresponsive and immobile.[13]

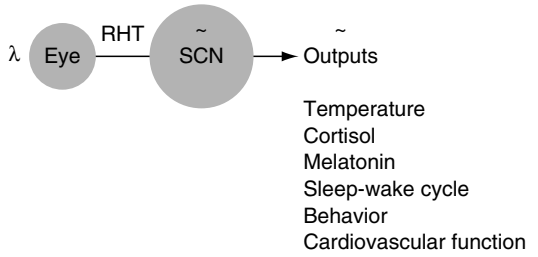

Figure 8–4. The input to the suprachiasmatic nuclei (SCN) is via special retinal receptors that form a synaptic connection to the retinohypothalamic tract, which carries light information to the SCN. These light receptors do not form synaptic connections with the optic nerve, and they transmit no visual information to the CNS visual processing centers. Therefore, conscious light perception and SCN input are via distinct pathways; if either is destroyed, the other can remain fully functional. (From Rivkees S: Mechanisms and clinical significance of circadian rhythms in children. Curr Opin Pediatr 2001; 13:352-357.)

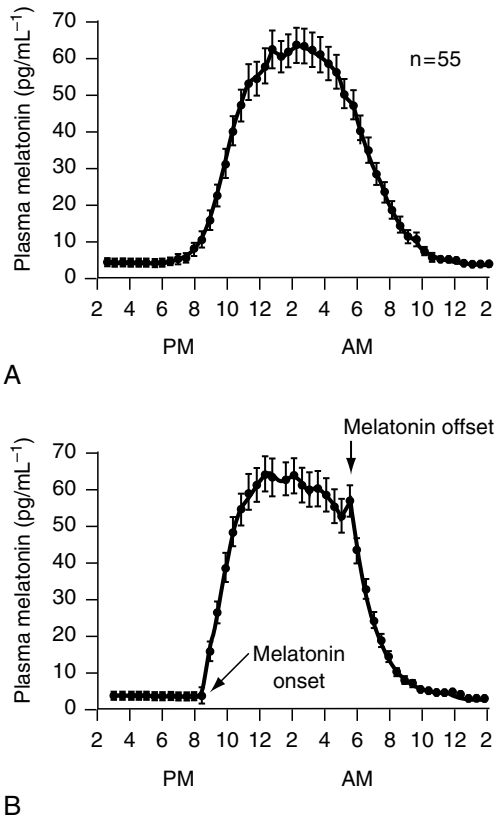

Figure 8–5. A, Melatonin secretory profile derived from averaging serum levels of melatonin. The result is a sinusoidal waveform with a periodicity of approximately 24 hours. **B,** Plotted values are derived from averaging forward and backward from each subject's time-locked melatonin onset and offset. B reveals melatonin as an on-or-off switch, demarcating the onset of biological night and the onset of biological day. (Redrawn from Wehr TA, Aeschbach D, Duncan WC. Evidence for a biological dawn and dusk in the human circadian timing system. J Physiol 2001;535:937-951.)

Point of Singularity

Each cycle of a circadian rhythm has an acrophase and a nadir (see Fig. 8–1D). The circadian nadir is significant: it is near the minimum of body temperature. Before this time, light has a phase-delaying effect, and after this time, light has a phase-advancing effect[19] (see Fig. 8–2A). Sometimes referred to as the point of singularity, the circadian nadir is coincident with the beginning of the rises of core body temperature, cortisol secretion, and the proportion of sleep occupied by rapid eye movement sleep. Exposure to bright light centered at the point of singularity significantly reduces the amplitude of core body temperature, plasma cortisol secretion, and melatonin secretion.[20]

Forbidden Sleep Zone

The "forbidden sleep zone" immediately precedes the onset of biological night. This is the time at which sleep is least likely to occur during a circadian cycle (see Fig. 8–2B). This 1- to 3-hour period is well established in human adults and adolescents. Because the forbidden sleep zone precedes the normal hour of sleep, many individuals with delayed sleep phase have difficulty advancing their hour of sleep despite sleep deprivation and daytime sleepiness.[21,22] Although forbidden sleep zones have not been studied in children, they appear to be particularly robust, as even children who are sleepy enough to fall asleep in school are not able to begin nighttime sleep at an earlier hour.

Circadian Outputs

An extremely large number of biologic, behavioral, cognitive, and emotional factors demonstrate consistent and predictable circadian rhythms. Core body temperature (see Fig. 8–1A), hormone secretion, and cell metabolism are among the better-known biologic parameters that demonstrate a circadian rhythm.[23] Human performance is well documented to demonstrate a circadian rhythm, and a variety of measures of cognitive skills show circadian changes in performance. Mood and emotions also follow predictable circadian patterns.[24,25] It is currently believed that most of our organs contain their own clock mechanisms, and that each of these maintains a synchronous relationship with the body's master clock via outputs from the SCN.[26]

Phase Shifts

Only disrupted phase, and no other aspect of the circadian rhythm, is considered a circadian sleep disorder. The phase of the circadian rhythm is synchronized with environmental time by a variety of zeitgebers (or time givers, and thus clock setters), principally bright light, but also including the timing of sleep and the timing of social contacts. Suitably timed exposures to bright light result in large shifts in the circadian phase.[27] In contrast to bright light (and melatonin), most other factors have only weak and inconsistent effects in shifting circadian phase.[28]

The phase-shifting effect of bright light (or any other zeitgeber) requires not only that it be delivered at a suitable time (see Fig. 8–2A), for sufficient duration, and at necessary intensity, but also that the individual not be exposed to light at times where the phase-shifting effect would be in the opposite direction.[29] For example, exposure to bright light during normal hours of morning sleep (after the point of singularity) will not result in a phase advance unless darkness is present during the earlier (evening) time interval to which sleep is to be phase advanced.

It appears that both light of ordinary room intensity[30,31] and daytime napping[32] are capable of inducing a small phase shift. These so-called weak zeitgebers[33] have been demonstrated to change circadian phase under conditions of constant routine, an experimental technique that eliminates all stimuli that would interfere with a phase shift. It is not clear how effective weak zeitgebers would be in shifting circadian rhythms under normal conditions.

Melatonin

Melatonin is secreted by the pineal gland during darkness, and the timing of its secretion appears to be under the control of the SCN.[34] Melatonin is sometimes referred to as the hormone of darkness. The endogenous rhythm of melatonin secretion is entrained by the light–dark cycle.[35] Light is able to both suppress and entrain melatonin production.[34] The normal timing of sleep is tightly coupled to the melatonin secretory profile. Melatonin is associated with sleep in diurnal mammals and with waking in nocturnal animals.

Melatonin administration and light exposure shift circadian phase in opposite directions. Thus, melatonin administration before DLMO results in a phase advance, and melatonin administration after the morning melatonin offset results in a phase delay. The phase-response curve to melatonin is similar to the phase-response curve to light but in the opposite direction.[36,37] Melatonin is more effective in altering the timing of circadian rhythms than that it is as a hypnotic.[38] The administration of exogenous melatonin alters the timing of endogenous melatonin secretion on subsequent days.[39]

In a constant-routine experimental paradigm, in which sleep is permitted for only 10 minutes, followed by 20 minutes of forced wakefulness for multiple 24-hour periods, sleep occurs only during intervals that coincide with melatonin secretion (greater than 10 pg/mL has been suggested as a minimal sleep-inducing melatonin level[4]). During intervals when melatonin is not secreted, sleep does not occur.[40]

The nocturnal onset of melatonin secretion is time-locked in humans to the opening of the nocturnal sleep gate: as melatonin secretory levels increase, body temperature falls. In a variety of free-running conditions, sleep occurs only when body temperature is dropping or low. These findings suggest that melatonin participates in sleep–wake regulation in humans.[18]

Masking

The environment exerts influences that keep an individual entrained with local day and night. These are exogenous influences that "mask" the body's endogenous circadian rhythm. Masking is so universally present that the body's circadian rhythm may be observed only under extremely controlled experimental conditions that eliminate the multiple zeitgebers of everyday life that keep all of us entrained. The timing of bright and dim light exposure, social activities, exercise, and meals all induce a masking effect.[41] Some degree of masking is occurring continually in all mammals whose endogenous circadian rhythm is not precisely 24 hours, as environmental zeitgebers synchronize circadian rhythms with the local hours of light and darkness.

Entrainment

Entrainment refers to an individual's hours of biological day and biological night being in synchrony, or in phase, with environmental day and night. Entrainment of circadian rhythms to an environmental schedule appears to be accomplished by a variety of factors, many of which have already been discussed: bright or dim light, social schedule, melatonin,[42,43] social activities,[44] and exercise.[45] Bright light induces greater entrainment than dim light; specifically, exposure to bright light induces a greater evening drop and morning rise in core body temperature. Daytime exposure to bright light also results in an advance in the circadian rhythm of body temperature compared to dim light.[46] These findings suggest that both dim and bright light entrain an organism to environmental phase, or time, but that bright light further enhances entrainment by inducing a greater amplitude of the temperature rhythm and an earlier rise in core body temperature. These findings suggest that children and adolescents with sleep initiation problems would benefit from daytime bright light exposure.

Effect of Indoor Light on Phase

The light of dawn (an average of 155 lux, similar to indoor lighting) is sufficient to induce a phase advance in normal subjects. It is also sufficient to prevent phase delay in subjects living in constant dim illumination.[47] Subjects kept in constant dim light (as opposed to timed indoor light) for 21 days who had knowledge of clock time and who had social cues in a group setting demonstrated free-running circadian rhythms, with a periodicity of 24{1/4} hours in melatonin and temperature rhythms.[48] This study shows that normal individuals may not be able to remain entrained to environmental time in the absence of timed light as a zeitgeber. Ordinary room light is capable of shifting the rhythms of temperature, melatonin,[49] and cortisol, indicating that the master circadian pacemaker has shifted in response to indoor light.[15,31] Both temperature and hour of sleep shifted to the earlier phase, indicating a change in the output of the master clock, similar to results observed in studies using bright light. It has also been shown that the timing of exposure to normal room light modulates the effect of bright light on circadian

phase, such as room light exposure during biological night, including television sets and computer monitors. This suggests that even in the presence of normally timed bright light, indoor light after or before normal daylight hours may induce a phase shift in the circadian rhythm.[50] These studies collectively indicate that indoor room light is sufficient to continually exert weak influences on circadian rhythms, but that it is insufficient to abruptly switch rhythms to a vastly altered sleep–wake schedule.

Resetting Circadian Time in Children

The phase-response curve (PRC), or the degree to which the circadian rhythm will be advanced or delayed, is based on the time at which bright light or melatonin is administered. Typically, the advance or delay of the circadian system is measured in the number of minutes that the circadian temperature nadir is advanced or delayed.

Timing of Light

The PRC shows that there is virtually no change in circadian rhythms (for example, timing of the temperature nadir) induced by exposure to light during the middle of the circadian "day"; on the other hand, there is maximal responsiveness when exposure occurs immediately before or after the temperature nadir.[51] Other investigators have found that under certain experimental conditions, light delivered at any time during the circadian day had a slight phase-shifting effect.[50] At about the time of the temperature minimum (point of singularity), a switch is thrown, and at this point light changes from having a phase-delaying to a phase-advancing effect: immediately before the temperature minimum, light has its maximal phase-delaying effect, and immediately after the temperature minimum, light has its maximal phase-advancing effect.[52]

Intensity of Light

The intensity of the light greatly influences the magnitude of the response, with bright light (about 5000 to 10,000 lux) having a much greater effect than normal room light (100 to 200 lux). Even dim light (less than 100 lux) might have a slight effect on shifting circadian rhythms.[53] The timing of sleep and darkness is as important as the timing of the bright light.[54]

A homologous phase-response relationship probably exists for melatonin and circadian rhythms, in which melatonin has the opposite effect of light: evening melatonin would advance the circadian rhythm and morning melatonin would exert a phase-delaying effect.[22] A single dose of melatonin properly timed is capable of advancing the human circadian clock.[55] In subjects living in constant dim light for a month, melatonin administered 2 hours before the temperature acrophase had a maximal effect on advancing the circadian rhythm.[34] Melatonin synthesis normally begins about the hour of sunset; in indoor-living humans, it typically begins to be present in plasma shortly after sunset (about 8 PM to 9 PM) and gradually rises to a peak about 3 AM to 4 AM, followed by a decline in plasma concentration to near zero by 9 AM. Both DLMO and melatonin offset have been found to be as reliable as core body temperature in estimating circadian rhythms.[3]

DEVELOPMENT OF CIRCADIAN RHYTHMS

In Utero and in the Neonatal Period

Some aspects of circadian rhythm appear to begin in utero in mammalian species. The mature circadian rhythm system requires connections from a fully functioning SCN to retinal inputs and to multiple targeted outputs. The circadian system is not fully functional at birth in most mammalian species. However, circadian rhythms begin in utero as the fetus becomes entrained to the mother's rhythm. From the standpoint of the fetus, this is an exogenous rhythm, externally imposed by factors such as maternal temperature or melatonin, prior to the development of the fetus's own fully developed SCN. In mammals, maternal melatonin and the maternal circadian temperature cycle convey information about environmental time. In some species, the retinohypothalamic tract transmits light information to the fetal SCN in utero, which is capable of becoming entrained to environmental light shortly prior to birth. However, light appears to be a less potent entraining factor in utero than maternal melatonin secretion.[56]

The Suprachiasmatic Nucleus

Neurogenesis of the SCN occurs 3 to 5 days before birth in rats and hamsters, respectively.[57,58] If a pregnant hamster is injected with melatonin the day before delivery, after weaning (on day of life 20) the midpoint of the pups' subjective *night* will coincide with the time of the injection. If the pregnant hamster is injected with a dopamine agonist, after weaning the midpoint of the pups' subjective *day* will coincide with the time of the injection. This demonstrates that dopamine and melatonin either are, or mimic, maternal entraining signals that represent day and night.[59,60]

The responsiveness of a pup's circadian clock to melatonin and dopamine agonist injections is gone by day 4 of life, replaced by an equally robust response to light (subjective night in rodents) and darkness (subjective day in rodents).[61] If two groups of pregnant hamsters are injected with a dopamine agonist 12 hours apart, the circadian rhythms of the two groups will be 12 hours out of synch on the day of weaning, demonstrating that the prenatal dopamine agonist set the phase of the offspring's circadian rhythms.[60] In rats, at about the same time—the end of the first week of life for the rat pup—the SCN develops the ability to be entrained by light. At this time, the circadian rhythm of *N*-acetyltransferase first appears.

The human SCN develops early in gestation, and circadian rhythms are present in the fetus and newborn. The circadian system seems to be functional in human fetal life and can receive circadian inputs through the mother.[62]

Uniqueness of SCN Tissue

For the lateral geniculate nucleus (LGN) to develop normally, afferents from the retina must innervate LGN cells during development. In visual deprivation studies, LGN hypertrophy results from interruption of retinal afferent fibers. Visual input from the retina is crucial in cell development and neural arborization in the LGN, as in most other CNS structures that are part of a sensory system. In contrast, there is no evidence that afferents from the retinohypothalamic tract, the raphe, or the intrageniculate nucleus influence the development of the SCN. Lesioning afferent fibers does not result in SCN hypotrophy. No other tissue takes on pacemaker properties if the SCN is enucleated early in development.[63,64]

Pacemaker properties of SCN cells are intrinsic: SCN fetal tissue develops its intrinsic rhythmicity even if transplanted to a totally different environment, such as the anterior chamber of an adult eye.[65] Fetal SCN tissue may be minced prior to transplantation, destroying specific spatial relationships, yet intrinsic rhythmicity develops normally.[66]

Role of Melatonin in Development

When the fetus's SCN begins to function, melatonin from the mother is probably the principal factor entraining it to the prevailing light–dark cycle.[67] Even when a pregnant mother is kept in constant light, the mother's rhythm and the rhythms of her offspring demonstrate a consistent phase relationship with each other.[68] This indicates that entrainment of the newborn to its mother results from intrauterine factors, especially when environmental zeitgebers are absent.

Nonphotic Zeitgebers in Development

In the absence of light cues for day and night, social contact may act as an entraining factor in developing mammals. Mice born and raised to the age of weaning in constant lighting conditions remain entrained to their mother's circadian rhythm. The mouse pup's daily onset of wheel running (nighttime) is entrained to the mother's termination of nursing, and therefore, the pups time of wheel running coincides with the mother's absence. In constant lighting conditions, the mother's return is taken by the pups as their rest time and her absence as their wake time.[67]

The newborn's temperature and melatonin secretory rhythms are in phase with environmental night and day, probably resulting from infant–mother synchronization. Feeding and rest–activity synchronization to mother and environment develop rapidly during the neonatal period.

In the First Year of Life

From birth to 6 months, the human infant develops robust circadian rhythms. The retinohypothalamic tract is present in humans before birth, and plasma melatonin demonstrates a rhythm

influenced by light within the first 2 days after birth.[69] Human rhythms are in phase with their environment when they appear, suggesting entrainment that precedes the ability to measure them. The SCN may be functioning before birth in humans but may not yet have developed output-entraining mechanisms. Human fetal rhythms are entrained to those of the mother, and the probable synchronizing substance is melatonin.[70] The human fetus shows a rhythm in heart rate and fetal movement activity that is also circadian.[71]

A weak circadian rhythm, showing newborn-mother entrainment, is observable in 24-hour consecutive plots of the infant's tympanic membrane temperature during days of life 1 to 14.[72] This implies that some degree of entrainment of the circadian rhythm of temperature has occurred in utero in the human fetus. If a human infant is exposed to only sunlight (no incandescent or florescent light) for the first 6 months of life, the sequential development of behavioral and physiologic properties of the infant's circadian rhythm become evident.[72] The circadian rhythm of temperature appears first, soon after birth, and becomes statistically significant within 1 week. Most apparent in 24-hour temperature plots of the first 2 weeks of life are a morning increase and an evening fall in temperature. The wake circadian rhythm appears soon after, attaining significance at day 45, approximately the same time that increased melatonin concentration begins to occur at sunset (DLMO, defined as salivary concentration greater than 20 pg/mL, equivalent to adult levels).[72]

The circadian rhythm of sleep appears last, attaining significance after day 56. Ninety- to 120-minute zones of sustained wakefulness first appear in the second month of life, after awakening and prior to sleep onset (forbidden sleep zone). The infant's nocturnal sleep-onset is coupled to sunset before day 60, and subsequently it is coupled to family bedtime, giving evidence of initial photic entrainment followed by social entrainment. Even in the absence of artificial light after sunset, the infant's sleep onset time tracks the family's schedule, as the infant remains awake for 1 to 3 hours every night in darkness.[72] Actigraphy monitoring of rest–activity cycles in the 3-week-old human infant also shows a circadian rhythm.[73]

Before sleep or wake demonstrates a circadian rhythm, the infant's morning awakening appears to become entrained to the rise in body temperature, and the two appear to remain coupled. Morning entrainment of awakening to rising body temperature appears to precede the coupling of sleep onset to sunset; dawn is a more powerful zeitgeber than dusk. A coupling of sleep onset to evening darkness first appears on a consistent basis during week 7 of life. A proclivity for sleep to occur during the night and wake to occur during the day is present in the first weeks of life as well. By week 14, the infant has developed a wake maintenance zone beginning at sunset and continuing for 1 to 3 hours.[72]

By 6 months of life, the human infant, when exposed only to sunlight, is entrained to both it and the social rhythm of the household. Maintenance of wakefulness zones are apparent as the infant remains awake after sunset.[72] Just as the organization of sleep stages attains adult criteria by age 6 months,[74] the human circadian rhythm displays period, amplitude, and phase activity at 6 months of age that are similar to these elements in adult human circadian rhythms. It appears that circadian rhythms are one of the earliest maturing physiologic-behavioral systems.

In the Preschool Child

Little research is available on the preschool child's circadian rhythms, probably because this is a period when aberrations and idiosyncrasies are more readily tolerated due to the absence of social scheduling requirements. It appears that preschool children are behaviorally similar to preadolescents, who are relatively phase advanced compared to adolescents.[75] The preschool child frequently becomes entrained to maternal or familial rhythms before becoming synchronized with a school schedule.

In the School-Aged Child

Remaining awake later on weekends and sleeping to a later hour has a phase-delaying effect, making it more difficult for the school-aged child to initiate sleep on Sunday night and to awaken on Monday morning.[76] This effect (remaining awake later and subsequent phase delay) may be greater over extended school vacations. During preadolescence in most children, sleep gradually becomes more delayed with respect to biological night, resulting in a

propensity to initiate sleep and awaken at a later hour despite little change in tau, or period length. Adolescents are better able to sleep after their body temperature rises and to remain awake after body temperature falls than younger children.[77]

Carskadon and colleagues[2] measured the circadian rhythm duration of 12- to 15-year-olds by having them follow a 28-hour day for 12 consecutive days. They were in dim light for two thirds of the 28 hours (waking period) then in darkness the remaining third of the time (sleep period). Because the human circadian clock is unable to synchronize to the 28-hour schedule, the timing of sleep and waking become "uncoupled" from the body's temperature and melatonin rhythm. In this protocol, measurement of the time from one temperature or melatonin peak to the next indicates the unmasked cycle length of the body's clock. The circadian rhythm duration of both temperature and melatonin was found to be 24.3 hours, longer than 24 hours, but similar to that found in older individuals.[2] This study demonstrates that the age-related, adolescent "night owl" propensity, or tendency toward delayed sleep and awakening, does not result from a longer adolescent clock cycle but must be caused by other factors, such as the timing of sleepiness with respect to the circadian temperature cycle.[7]

Another study found that 10th grade and 3rd grade children sleep the same number of hours on weekends, about 9{1/4} hours, but the bedtimes and wake-up times of older children are 2 hours later than those of younger children. This indicates that the biological clock of the late adolescent is set 2 hours later than that of the younger child, and that sleep need has not changed significantly from early childhood to adolescence.[75]

CONCLUSIONS

Circadian rhythms in humans develop in utero, under control of maternal melatonin early in gestation, and later under control of the fetus' developing SCN. Light suppresses the secretion of melatonin, a hormone that is secreted in darkness and is related to biological night in humans. Melatonin levels are higher at approximately the time when sleep occurs. The pacemaker system (anatomically centered in the SCN) receives information about the presence of light, which suppresses melatonin secretion, from the retina. The timing of the pregnant mother's exposure to light affects her secretory melatonin levels and those of the fetus. If the mother's light exposure during the later portion of gestation is restricted to daytime hours, this could increase the likelihood that the newborn will first express a sleep-wake pattern in synchrony with environmental light and dark.

Circadian rhythms of some aspects of human physiology are present at birth. A sleep–wake circadian rhythm that is quite robust emerges in the first 6 months of life, including the hour at which sleep begins and ends. The history of an individual's recent light exposure determines a specific time at which the circadian clock permits sleep to begin (biological night) and as well as a time at which an individual is likely to awaken (biological day).

The greater the proportion of the 24-hour period that is occupied by darkness (biological night), the longer is the duration of melatonin secretion, which is associated with an increase in the number of hours of sleep. Thus, both the circadian rhythm (timing) of sleep and the homeostasis (amount) of sleep are influenced by light exposure. Data from healthy human subjects suggest that sleep time increases if the duration of environmental night (dark period) is increased. The same data suggest that sleep time decreases if the duration of environmental night is decreased. Humans are biologically and behaviorally equipped to accommodate to long nights in winter and short nights in summer.

The timing of biologic rhythms is also partially under the control of factors other than light, especially if exposure to bright light is curtailed. The timing of social and family activities may influence the timing of sleep. Thus, regular timing of family activities, including meals and bedtimes, is likely to facilitate the development of more regular rhythms in a human infant, child, or adolescent.

Indoor light can be disruptive to sleep. We possess a circadian mechanism that has not adapted to the variety of light- and sound-emitting devices that may be present in many households during the hours of night. The presence of indoor light allows each family (or individual) to select its hours of darkness (and quiet), a phe-

nomenon that could be detrimental to the optimal expression of sleep in children. In effect, artificial light enables the contraction of environmental night, possibly decreasing a child's total hours of sleep.

A family's timing of activities and their hours of light exposure influence when and how much a child sleeps throughout development. The encroachment of (artificial) daytime into hours historically reserved for sleep has unknown influences on human development, as this is a recent phenomenon from a biologic perspective.

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