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The Development of Circadian Rhythms: From Animals To Humans

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Introduction

Circadian rhythms are endogenously generated rhythms with a period length of about 24-hrs. Evidence gathered over the past decade indicates that the circadian timing system develops prenatally and the suprachiasmatic nuclei, the site of a circadian clock, are present by mid-gestation in primates. Recent evidence also shows that the circadian system of primate infants is responsive to light at very premature stages and that low intensity lighting can regulate the developing clock. After birth, there is progressive maturation of the circadian system outputs, with pronounced rhythms in sleep-wake and hormone secretion generally developing after two months of age. Showing the importance of photic regulation of circadian phase in infants, exposure of premature infants to low-intensity cycled lighting results in the early establishment of rest-activity patterns that are in phase with the 24-hour light-dark cycle. With the continued elucidation of circadian system development and influences on human physiology and illness, it is anticipated that consideration of circadian biology will become an increasingly important component of neonatal care.

The Circadian Timing System

Circadian rhythms are endogenously driven rhythms with a period length of about 24-hrs[1-3]. Notable examples of circadian rhythms include the sleep-wake cycle and daily rhythms in hormone production. Circadian rhythms are also involved in the pathogenesis of illnesses, such as reactive airway disease and myocardial infarction[3-7].

The system responsible for the generation and regulation of circadian rhythms is the circadian timing system. This neural system consists of a biological clock, input pathways, and output pathways[1]. The paired suprachiasmatic nuclei (SCN) in the anterior hypothalamus are the site of a biological clock. The SCN are located above the optic chiasm at the base of the third ventricle[8]. The SCN exhibit endogenous rhythmicity and have a period of oscillation close to 24-hrs. Peripheral clocks also play a role in circadian rhythm expression[9-11].

Lesion studies in rodents provided the initial evidence that the SCN are the site of a circadian pacemaker[8]. *In vivo* and *in vitro* studies have since shown day-night rhythms in electrical activity, metabolic activity, and gene expression. Transplantation of fetal SCN cells into SCN-lesioned animals restores rhythmicity to the recipient further supporting that the SCN contain

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a biological clock[8]. Circadian oscillations have been seen in individual rodent SCN cells, and expressed rhythmicity reflects the collective oscillations of many SCN cells[12, 13].

Because SCN oscillations are not exactly 24-hrs, it is necessary to reset the circadian pacemaker each day to prevent endogenous clock oscillations from drifting (or free-running) out of phase with the external light-dark cycle. Input pathways relay photic information from the retina to the SCN to synchronize (or entrain) the oscillations of the clock to the 24-hr light-dark cycle[14, 15]. A direct pathway from the retina to the SCN, the retinohypothalamic tract (RHT), has been shown to be both necessary and sufficient for photic entrainment[14]. The raphe nucleus also influences SCN function via serotinergic projections[14].

Output pathways are responsible for the overt expression of circadian rhythms. Several discrete neural pathways projecting from the SCN to several hypothalamic and non hypothalamic sites have been defined[16-18]. Via these pathways, the circadian system acts to broadly influence neural physiology. Output pathways of the circadian system also regulate the rhythmic production of several hormones including melatonin and cortisol[4, 5, 16-18].

The Primate Circadian System

Several lines of evidence support that the paired SCN are the site of a biological clock in primates. Similar to rodents, the primate SCN are located above the optic chiasm at the base of the third ventricle[19]. In contrast to rodents, human SCN cells are not densely clustered making the nuclei less visually apparent[19-21]. However, using probes for melatonin receptors and SCN peptides, the human SCN can be identified[19-21]. Using DG, day-night oscillations in SCN metabolic activity have been detected in squirrel monkeys and baboons [22-24].

Lesion studies performed in the early 1980s suggested the presence of a circadian pacemaker outside of the SCN in monkeys[25]. However, analysis of these reports revealed that either the completeness of the lesions was not verified, or monkeys were not studied in constant conditions[26]. Reexamination of this issue challenges the existence of primate circadian pacemakers outside the SCN. Squirrel monkeys with total SCN lesions show a complete absence of circadian rhythmicity when animals are monitored in constant conditions[26]. Supporting that the SCN are the site of a circadian pacemaker in humans, tumors and congenital lesions in the SCN region result in the loss of temperature rhythms and organized sleep-wake patterns[27, 28].

The RHT has been anatomically characterized in prosimian (lemurs, shrews) and simian (squirrel monkeys, rhesus macaques, baboons, chimpanzees and apes) species[19]. This tract also has been identified in studies of postmortem human specimens using techniques that label degenerating retinal axons[29, 30]. Although it was suggested that cutaneous light exposure can influence circadian function[31], there is little support for the notion that there is extraretinal photoreception in mammals[32-34]. Furthermore, other investigators have failed to reproduce phase shifting effects of cutaneous light exposure[22].

Outputs of the primate circadian system have been widely characterized in human clinical studies. Many day-night rhythms have been documented[4, 5, 33]. Several of these rhythms have been shown to persist in constant conditions indicating that they are true endogenously generated circadian rhythms. Notable examples of circadian rhythms include the sleep-wake cycle, daily rhythms in body temperature, and day-night rhythms in cortisol and melatonin production[4, 5, 33]. Day-night differences in gonadotropin, testosterone, growth hormone and thyrotropin secretion are also present[35, 36].

Development of the Primate SCN

Although rodent studies have led to our understanding of developmental circadian physiology[35-38], notable differences between rodents and primates have prevented the extension of rodent data to clinical care. In general, rodents are more immature at birth than humans. Differences in the sensitivity to light and other aspects of circadian physiology between humans and rodents also have been observed. However, based on evidence gathered over the past decade, it appears that the circadian clock in the SCN forms and begins oscillating *in utero* in primates.

In squirrel monkeys, SCN neurogenesis occurs early in gestation over days 27-48[39]. Because monkey and human embryonic development are very similar over the first 100 days of gestation[40], it is therefore likely that the human SCN neurons form early in gestation.

It is not currently known when the primate SCN are first apparent morphologically. Yet, using [^{125}I]melatonin and [^{125}I]SKF38393 to label the nuclei, the human SCN have been detected at gestation week 18 [41, 42] (Figure 1).

Functional studies suggest that the primate SCN oscillate prenatally. Studies of squirrel monkeys reveal day-night differences in SCN metabolic activity at the end of gestation[43]. It is not known if SCN oscillations are present at earlier ages. The physiologic processes influenced by the fetal clock have yet to be elucidated in primates.

Similar to rodents, the timing of the onset of labor and birth in humans is influenced by the circadian cycle with peak incidences between midnight and the early morning[44]. However, we do not know if the fetal clock plays a role in the circadian gating of birth in humans.

Immunocytochemistry studies show that SCN maturation continues after birth[45]. The SCN contain distinct populations of neurons that express arginine vasopressin or vasoactive intestinal polypeptide[45]. In term infants, the number of vasopressinergic neurons is 20% of the number present in adults[45]. It is not until one year of age that infants and adults have comparable vasopressin neuron numbers[45]. The number of vasoactive intestinal polypeptide containing SCN cells also increase after birth[45].

Development of Primate Photic Entrainment

A critical issue in knowing if environmental cycles need to be considered in the care of infants is knowing when the primate circadian system becomes functionally responsive to light. The RHT has been identified in a 36 week gestation human newborn[46]. However, because of human study limitations, has not been possible to determine if the circadian clock of human infants is functionally responsive to light at birth.

Non-invasive methods used to examine regional changes in brain activity, such as function magnetic resonance (fMRI) imaging or positron emission tomography (PET), hold promise in being able to directly examine SCN function. In human adults, we have been able to observe acute increases in SCN metabolic activity after light exposure at night using ^{18}F-DG in PET studies[47]. However, because of the small size of the SCN, consistent visualization of SCN activity is difficult to achieve and these methods have not been applied to infants.

Because of human study limitations, we have studied baboons, which are excellent models for human infants, to provide insights into the developing human clock. By monitoring changes in SCN metabolic activity and gene expression (Figure 2), light responsiveness can be demonstrated at birth in term baboon infants[24]. The presence of the RHT can also be demonstrated[24].

By monitoring the effects of different lighting conditions on newborn baboon activity patterns, we have been able to show that newborn baboons are entrained by low intensity (200 lux) lighting[24]. These findings are similar to those seen in human adults showing that circadian phase can be regulated by low intensity (ca. 180 lux) lighting[48, 49]. Thus, it is likely that low intensity lighting, similar to that found indoors, can regulate the developing primate clock.

To determine when photic responsiveness first occurs in primates, we have studied premature baboon infants[50]. To our surprise, we find that the SCN are functionally innervated by the retina at stages equivalent to 25 wks post-conception human infants [50] (Figure 3).

The primate circadian system is therefore sensitive to light in very premature infants when postnatal survival with intensive support becomes possible.

Development of Expressed Rhtymicity

The development of expressed rhythmicity has received attention in both human and nonhuman primates. During pregnancy, day-night rhythms are observed for a variety of hormones (esterone and progesterone) and physiological parameters (uterine contractility) in mothers[51, 52]. In human fetuses, day-night rhythms in heart rate, respiratory rate, and adrenal steroidogenesis have been detected[51, 52]. However, these rhythms appear to be driven by the mother.

When term human infants are examined, day-night rhythms are difficult to detect in the neonatal period[47, 53-58]. Consolidated periods of activity and rest are not generally observed until after the first or second month of life. Activity plots of human newborns reveal that sleep is generally distributed over the 24-hr day during the first few weeks of life (FIGURE 3). At 6 wks of age, infants are awake more during the daytime than at night. By 12 wks of age, daytime sleep duration decreases further and much more sleep occurs at night. Importantly, although consolidated periods of rest and activity are not apparent until more than one to two months after birth, day-night differences in activity can be detected as early as one week of age in some babies.

At the age when day-night differences in infant activity become clearly apparent, day-night rhythms in hormone production are observed. Day-night rhythms in melatonin production can be detected at 12 weeks of age[59, 60]. Circadian variation in cortisol levels appears between after 3-6 months of age[61-63]. With advancing age, circadian rhythms have been detected for a variety of other hormones and circulating factors[64].

Because infant care influences activity patterns, it is possible that patterns of developing circadian rhythmicity in human infants reflects influences of caregivers rather than endogenous rhythmicity. Thus, to characterize the development of expressed rhythmicity in primates, we have examined the development of expressed rhythmicity in newborn baboons raised in constant conditions (continuous dim lighting, evenly spaced care)[24]. Similar to human infants, baboon infants do not manifest clear day-night differences in activity patterns in the early neonatal period (Figure 4). Yet, at one month of age, day-night differences in activity patterns are observed. Developing primate rhythmicity thus reflects maturation from a state of relative arrhythmicity to rhythmicity over the first few months of life.

As in rodents, it appears that infant circadian phase is synchronous with that of the mother in baboon and human infants. However, in some humans and baboons[24, 65], infant phase may be out of synchrony with that of the mother at birth. Thus, whereas there is maternal-infant synchrony of circadian phase in most primates, it may not be universal.

Rhtymicity in Premature Infants

The large number of premature infants hospitalized for extended periods has greatly facilitated studies of rhythmicity in preterm infants. Over the past decade, studies of patterns of infant activity, heart rate, temperature, and sleep state have not surprisingly flourished[56-58, 66]. Several of these studies have revealed the presence of ultradian rhythms (rhythms with period lengths of much less than 24 hrs). Endogenously driven circadian rhythms, however, are not clearly apparent.

When temperature and heart rate are studied beginning at a postconceptual (PC) age 24-29, circadian rhythmicity is generally not apparent even at 17 weeks after birth[67]. Studies of preterm infants at PC 32 weeks, have failed to detect day-night differences in sleep patterns whereas some differences are noted in term infants[68]. Analysis of temperature, heart rate, and activity patterns at PC 35 weeks have revealed ultradian rhythms, but no clear cut circadian rhythms[68-70]. Because feeding and physical contact influence infant temperature, heart rates and activity patterns, it is likely that infant care schedules drive the ultradian rhythms seen in preterm infants. These interventions may also mask the detection of circadian rhythms.

The Yale Neonatal Entrainment Study

Following the discovery that the primate circadian clock is responsive to light in very premature infants, we next assessed the effects of photic entrainment on premature infants [71]. In these studies, the development of rest-activity patterns was examined in human preterm infants exposed to continuous dim lighting or low-intensity cycled lighting before discharge from hospital to home.

In general, day/night differences in rest and activity are not apparent in hospitalized control infants (Figure 5), whereas day/night differences in rest and activity are seen in experimental infants. Over the first ten days at home, distinct day/night differences in activity are not seen in controls, but experimental infants are more active during the day than at night. It was not until 21-30 days after discharge that day/night activity ratios in control infants match those seen in experimental infants shortly after discharge. Yet, even at this age, experimental infants are considerably more active during the day as compared to control infants. Despite the differences in rest-activity patterns among groups, no differences in weight gain or change in head circumference are seen.

These observations show that exposure to low-intensity cycled lighting for 10 days before discharge induces distinct patterns of rest/activity in preterm infants that are in synchrony with the light-dark cycle that they will encounter at home. These effects are even more pronounced as soon as the child is discharged to home. In contrast, the appearance of rest/activity patterns in synchrony with the solar light-dark cycle is delayed in infants that have been exposed to continuous dim lighting in the hospital.

Other Studies of Lighting and Infants

Potential influences of cycled lighting on premature infants have been the subject of a few previous studies. In the Stanford Cycled Lighting Study, differences in circadian rhythms in temperature were not detected among infants exposed to either continuous dim lighting or cycled lighting before discharge [69, 70, 72]. These infants were studied 1 and 3 months after discharge. Because we observe that infants in both groups manifest similar circadian phase by 30 days of age, treatment effects on the rhythm of core body temperature may no longer be distinct after one month of age.

Other investigators have suggested that exposing infants to light/dark cycles improves infant weight gain. Mann and co-workers found that exposure to light/dark cycles before discharge resulted in better weight gain and more sleep over the 24-hour day than did chaotic lighting patterns[73]. These effects were seen 6 weeks after discharge and not sooner[73]. Because of this lag period, it has been suggested that the observed effects were not a direct result of cycled lighting exposure on the infant[72]. More recently, it has been suggested that exposing infants to light/dark cycles improves the in-hospital growth of babies if exposure occurs before 36 weeks of age[74]. Yet, the infants in near-darkness group in this study appeared more ill than the other groups. Considering that it is difficult to detect circadian activity in premature infants[47, 75], the potential mechanisms by which lighting could directly influence the growth of premature infants is not clear. By studying infants that were closely matched at enrollment, we failed to observe influences of lighting on growth either in-hospital or at home.

Previous studies have suggested that day/night rhythmicity is not apparent in prematurely born babies until nearly one month after term-birth age equivalency is reached (>42 weeks postmenstrual age)[69, 70, 72, 76]. These conclusions have been based on 24-48 hour assessments of rectal temperature and/or sleep patterns. However, using actigraphy to continuously monitor rest-activity patterns, we find that circadian phase can be detected in infants exposed to cycled lighting as early as a postmenstrual age of 34 weeks. In our previous studies of non-human primate infants reared in constant conditions, we also found that day/night differences in rest and activity were apparent shortly after term birth[24]. Most importantly, we find that day/night differences in activity could be detected several weeks before it was possible to detect circadian rhythms in core temperature using internal telemetry devices[24]. Thus, analysis of rest activity patterns may provide the earliest index of developing circadian rhythmicity in infants.

Nursery Lighinting Practices

The practice of nursery lighting has changed over the past several decades without a clear basis. Cycled lighting was often used in the hospital nurseries in the fifties and sixties. Yet, continuous bright lighting became favored when isolettes and neonatal intensive care units were introduced in the seventies. In reaction to continuous bright light, continuous dim light was introduced in the eighties and nineties, along with covering infant isolettes with blankets and quilts.

Although continuous dim lighting is the current practice in most nurseries in the United States, the scientific basis for this practice is not clear[77]. It has been suggested that ambient lighting may contribute to eye disease in premature infants[78]. Yet, rigorous clinical studies have failed to show adverse effects of low intensity lighting on premature infants[79-81].

Investigators who propose a NIDCAP (Neonatal Individualized Developmental Care Assessment Program) have suggested that since the womb is dark, infants should be dark-reared[82]. This approach overlooks the fact that prenatally the infant is exposed to maternal time-of-day cues that synchronize the fetal clock with the external light/dark cycle[37]. Rearing premature infants in the dark thus deprives babies of the time-of-day information that they would have received during full gestation. Data also show that the NIDCAP approach does not improve developmental outcome or sleep of premature infants[83, 84]. Thus, a rational approach considering the importance of circadian rhythmicity and environmental lighting cycles is needed in the care of hospitalized infants.

Summary

Increasing evidence indicates that the circadian timing system is a fundamental homeostatic system that potently influences human behavior and physiology throughout development (Figure 6).

After birth there is progressive maturation of the circadian system with day-night rhythms in activity and hormone secretion developing between one and three months of age. Recent evidence shows that the circadian system of primate infants is responsive to light at very premature stages and that low intensity lighting can regulate the developing clock. With the continued elucidation of circadian system development and influences on human physiology and illness, it is anticipated that consideration of circadian biology will become an increasingly important component of neonatal care.

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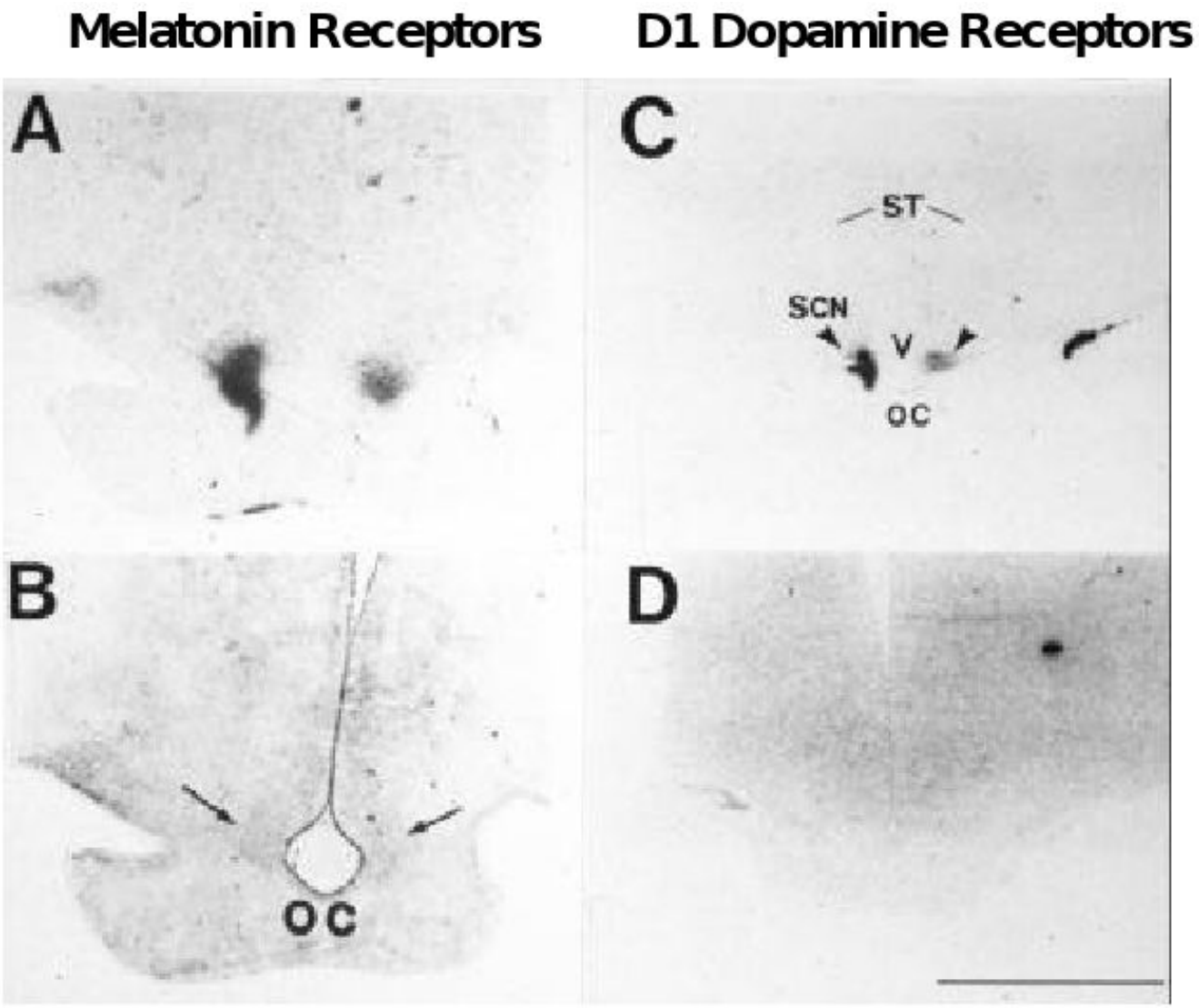

Figure 1.

A. Localization of [^{125}I]melatonin binding to the SCN of an 18-week gestation human fetus. Specific labeling is shown in black. B. The stained section used to generate the autoradiograph in A. Reproduced by permission from ref [33]. C. Localization of [^{125}I]SKF38393 binding to D1 dopamine receptors in the SCN of a 20-week post conceptual human infant. Specific labeling is shown in black. D. Non-specific labeling. Reproduced by permission from ref [34]. OC, optic chiasm; ST, striatum. Arrows identify the SCN.

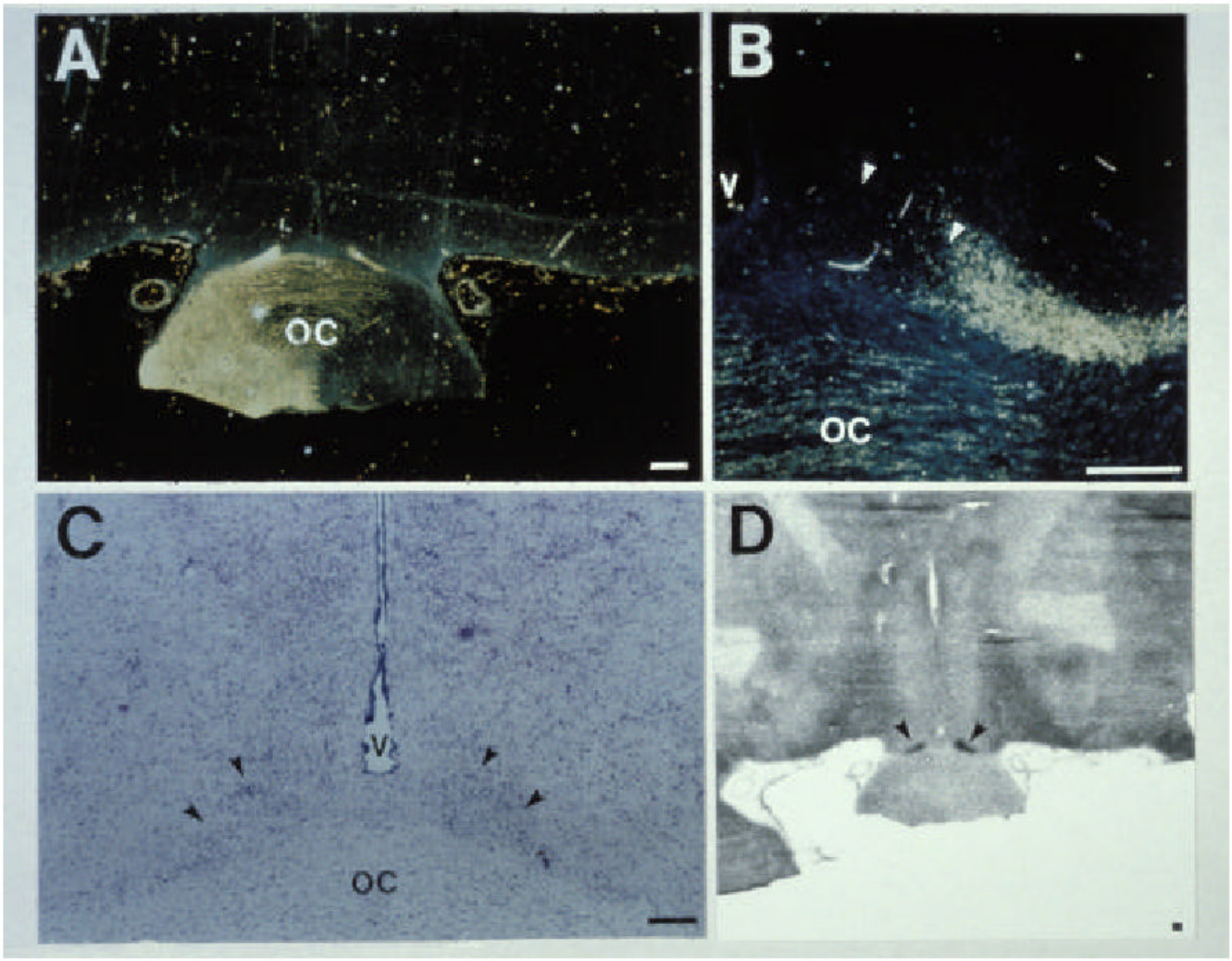

Figure 2.
Innervation of the SCN by the retinohypothalamic tract (RHT) in a newborn baboon infant. A. Low-power image showing labeling of retinal fibers in the optic chiasm by horseradish peroxidase. B. Adjacent tissue section showing the location of the SCN. C. High power image showing projections of the RHT into the right SCN. D. Autoradiographic image generated from [^{14}C]2-deoxyglocose uptake studies showing that light exposure at night induces increases in SCN metabolic activity. Areas of increased uptake are dark. Arrows identify the SCN. Scale bar = 5 mm. Reproduced by permission from ref [16].

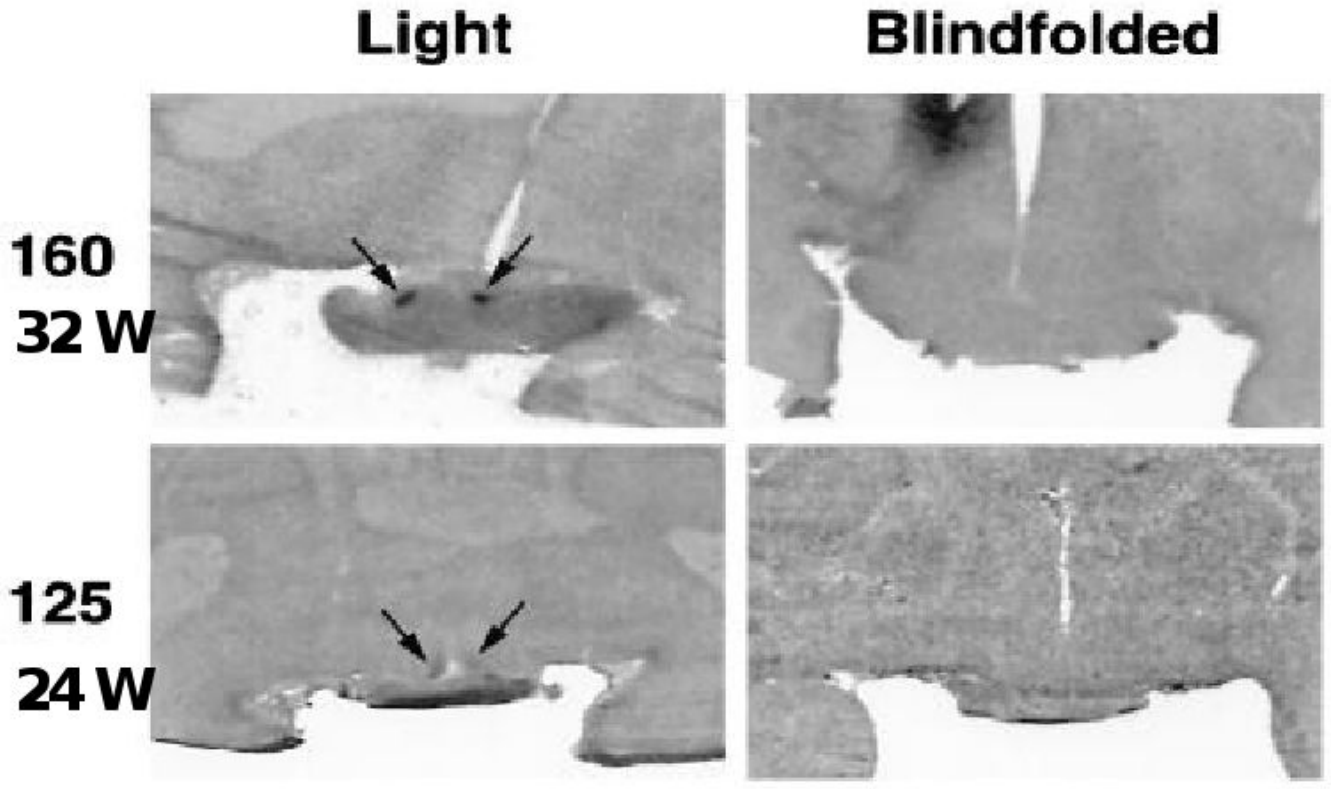

Figure 3.
Autoradiograph images of preterm baboon brain sections showing SCN DG uptake after light exposure at night. Animals shown were PC 160 or 125 and were either blindfolded or directly exposed to light. The images are obtained from mid-SCN levels. Arrows identify the SCN image. Reproduced by permission from ref [42].

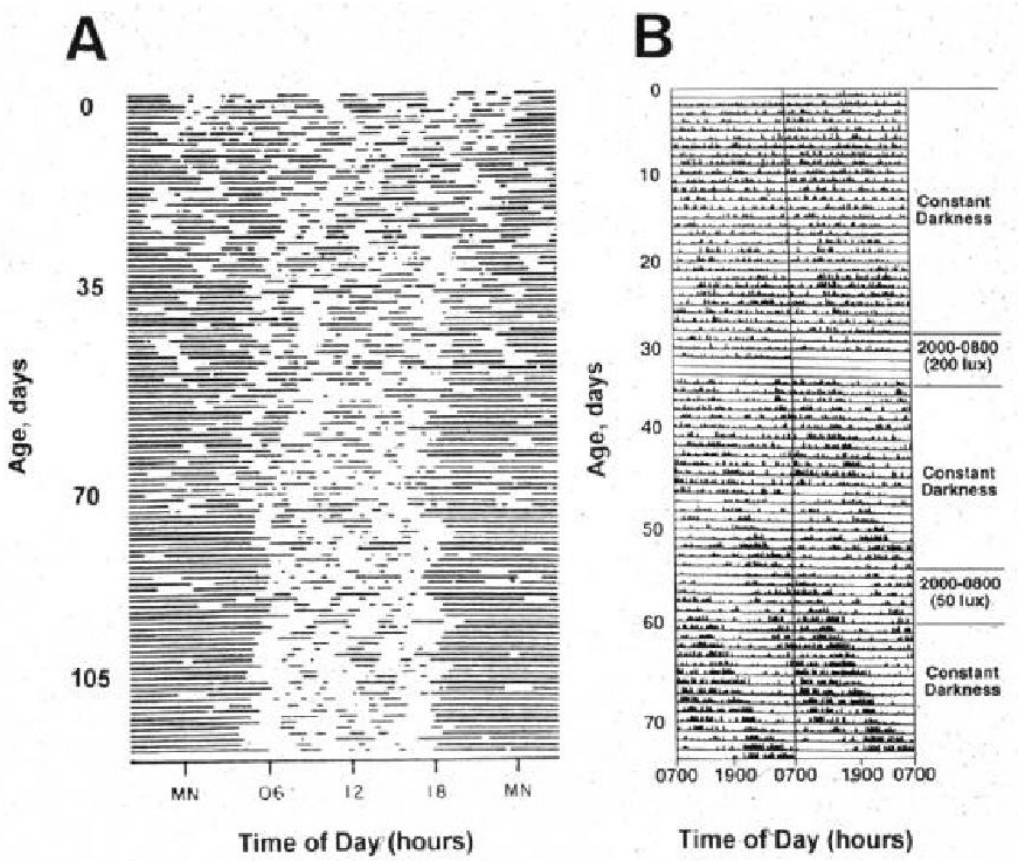

Figure 4.

Rest-activity patterns of a newborn human (A) and a baboon (B) infant (right). Double-plotted actograms are shown. In A, dark bars represent sleep. In B, dark bars represent activity. Please note that the circadian phase of the baboons infant was shifted by exposure to a 200 lux reversed light-dark cycle at 30 days of age, and much less so by 50 lux of exposure at 55 days of age. Reproduced by permission from ref [16].

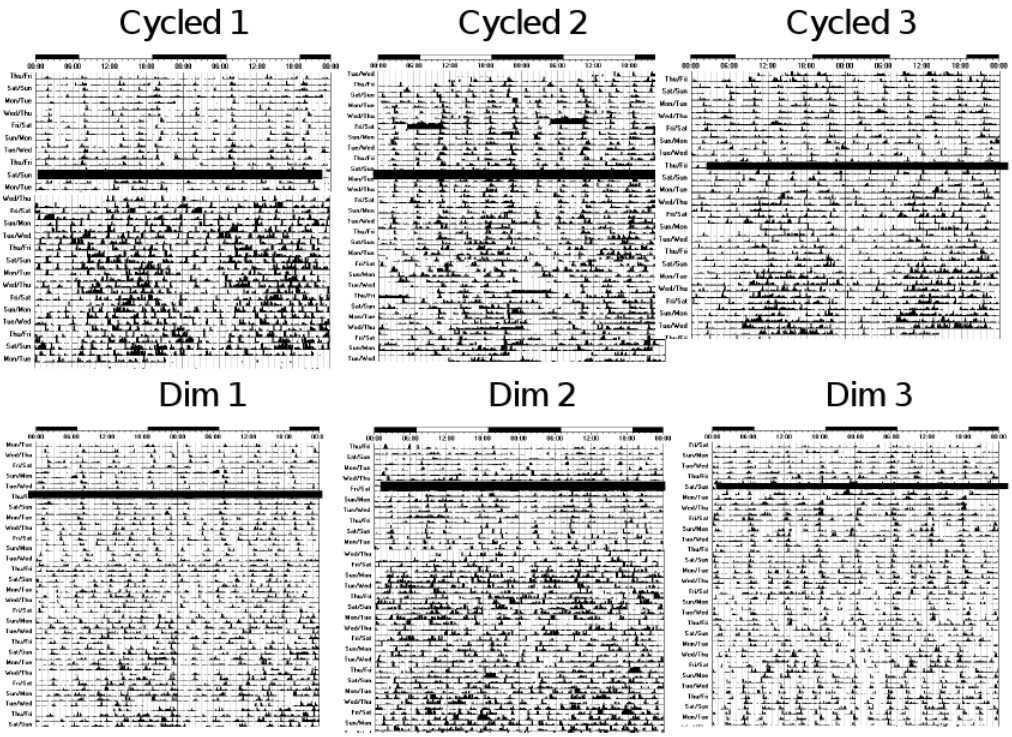

Figure 5.

Actograms of rest-activity in representative infants exposed to cycled lighting in the (top panels) or constant dim light (bottom panels). Dark bars represent activity; the same activity scale is used in each plot. The time of day is shown on top. The thick dark line in middle of plots depicts the date of discharge. Note that distinct patterns of rest and activity in the infants are more apparent after discharge in infants exposed to cycled lighting than dim lighting before discharge from the hospital. In infants exposed to dim lighting, day-night differences in rest-activity patterns in synchrony with the light-dark cycle are generally not apparent until about 20 days after discharge from the hospital.

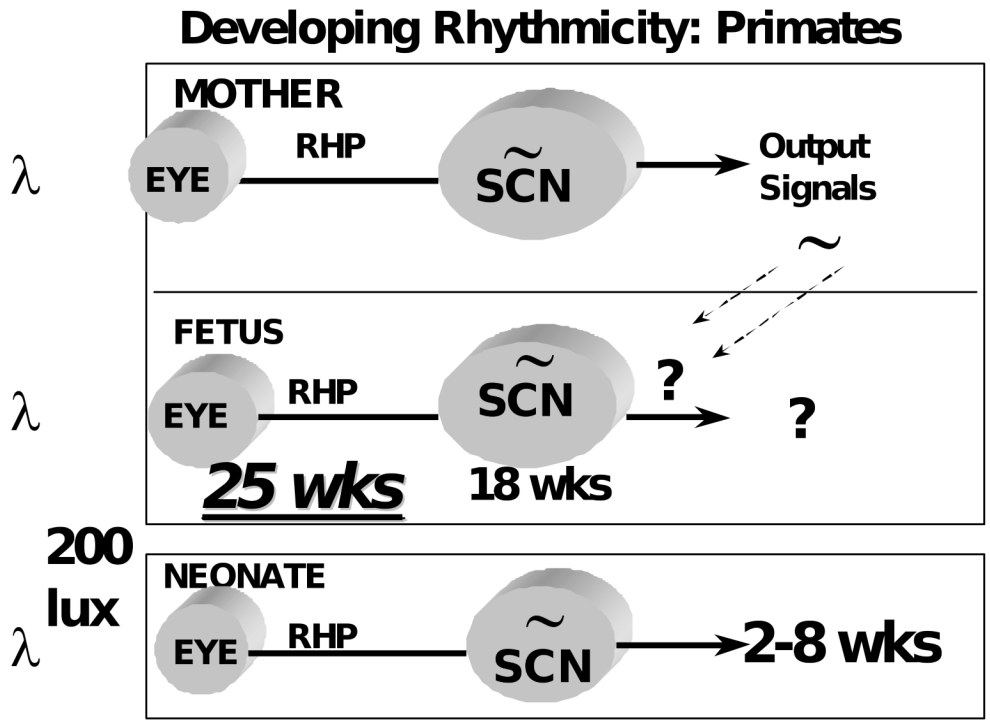

Figure 6.
Schematic representation of primate circadian system development based on studies of non-human primates. Estimated human ages are given.