The Development of Circadian Rhythms in the Fetus and Neonate

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The circadian time-keeping system is the neural system that allows predictive adaptation of individuals to the reproducible 24-hour day/night alternations of our planet. A biological clock, the suprachiasmatic nucleus, receives environmental information and imposes a circadian pattern to physiological functions. Since the suprachiasmatic nucleus develops early in gestation and circadian rhythms are present in the fetus and newborn, the circadian system seems to be functional in fetal life and can receive circadian inputs through the mother. The neonate moves to an environment in which the main time giving signal is the light:dark cycle. Teleologically, a term newborn should be fit to face this challenge. But this may be quite different for a preterm infant that trades the circadian environment to which it was previously exposed for the timeless environment of the Neonatal Intensive Care Nursery. Scientists and physicians should seek new experimental and clinical approaches to answer the challenging questions of perinatal chronomedicine.

The circadian time-keeping system is the neural system that allows predictive adaptation of individuals to the reproducible 24-hour day/night alternations of our planet. This system generates the 24-hour rhythms (circadian rhythms) present in almost every physiological function. A complex interaction of the biological clock with other brain nuclei, autonomic nervous system, and peripheral effectors governs circadian rhythms. Within an individual, the phase of the circadian rhythms of diverse physiological functions is distributed in given segments of the 24-hour day, creating an internal temporal order. Disturbance of such order accounts for the discomfort of jet lag and play a role in the decreased performance in shift work. Damage of the biological clock results in cognitive and behavioral disturbances.[1] We have limited knowledge about the role of this neural system in fetal and newborn physiology and about the potential impact of treatments in utero or of preterm birth on its development.

Several recent reviews have addressed the function and development of the circadian time keeping system.[2-5] Conceptually, this system can be described as formed by a biological clock receiving inputs from the environment and sending outputs that command overt circadian rhythms (Fig 1). In mammals, the clock resides in a paired structure, the suprachiasmatic nucleus (SCN), located bilaterally over the optic chiasm in the hypothalamus (Fig 2). A network of neurons forms the SCN. These neurons oscillate in vitro with periods from 20 to 28 hours and become synchronized to give the period close to (circa) 24 hours as displayed by SCN slices *in vitro* and by the SCN in vivo.[2] The molecular events determining neuronal oscillatory function in the 24-hour rhythm involve the expression of genes for at least 4 transcription factors that interact in a transcription/transduction feedback loop.[3] In animals, environmental information, mainly the light:dark (L:D) cycle, adjusts the period of the SCN oscillation to 24 hours and positions the phase of the oscillation in the 24-hour rhythm. Signals from the retina, conveyed by a glutaminergic monosynaptic pathway, the retinohypothalamic tract (RHT), act on some of the genes, shifting the phase of the

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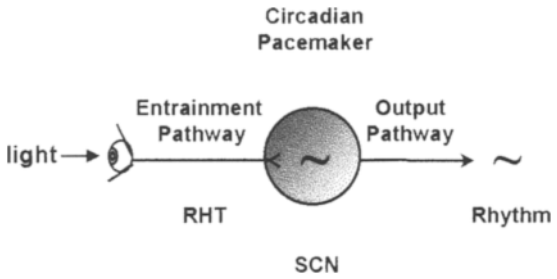

Figure 1. Schematic representation of the circadian timing system. SCN, suprachiasmatic nucleus; RHT, retinohypothalamic tract.

oscillation of the neurons and entrain them to the L:D cycle. Output signals from the SCN impinge on regulation of physiological functions resulting in endocrine (cortisol, thyroid stimulating hormone, gonadotropins, melatonin), cardiovascular (blood pressure, heart rate) biophysical (temperature) and behavioral (activity/rest, sleep/wake) circadian rhythms. SCN neurons contain the neuropeptides somatostatin, vasoactive intestinal peptide (VIP), vasopressin (AVP) and neurotensin. Efferent pathways from the SCN project to the subparaventricular zone, dorso, medial and ventromedial hypothalamic areas and paraventricular nucleus (PVN). The best-known pathway is the multisynaptic pathway controlling pineal function, which includes GABAergic connections from the SCN to the PVN, projections from the PVN to the spinal cord, and further connections to the cervical superior ganglion and the pineal.[6]

The control of adrenal cortex rhythms is mediated by synaptic contacts of SCN neurons with corticotropin releasing factor containing neurons of the PVN. An analogous pathway via the PVN and spinal cord to the adrenal cortex is involved in the control of the rat corticosterone rhythm.[7] In addition, SCN control of specific circadian rhythms may also involve endocrine SCN outputs.[8] A final result of these mechanisms is that in individuals exposed to the L:D cycle, the phase of a given rhythm will be similar for different individuals and rhythms will also be detected in the mean of the population. In the absence of L:D signals, either by exposure to constant light or constant dark or in blind people, individual rhythms persist but their period deviates from the 24-hour rhythm. Therefore, individuals will show differences in the phase of a given rhythm and such rhythm may not be detected in the population mean.[5]

Development of the SCN

Development of the SCN has been extensively studied in laboratory animals like rats, hamsters and sheep, whereas a limited amount of information is available in humans and in non-human primates.[9-11] Table 1 summarizes the information available on the development of the SCN in these species. Because developmental landmarks in the hamster SCN are similar to those in the rat SCN, they were not included in the table. Neurological development at birth differs notably between rats, humans, nonhuman primates and sheep. However, the fetal SCN is recognized by mid gestation in the 4 species (Table 1). Growth of the SCN has been studied systematically in rodents and sheep. In sheep, the SCN undergoes a period of rapid growth starting at about 40% of gestation that is followed by a period of neuronal loss to attain the final number of neurons at about 70% gestation. In the rat, the same events are completed by 90 % gestation.[9] In the human, Swaab et al[12] reported that the final number of neurons is reached after the first postnatal year. It is possible that this figure may not be precise, because these authors state that they had difficulties in determining the boundaries of the fetal SCN. In rats, humans and sheep AVP containing neurons are

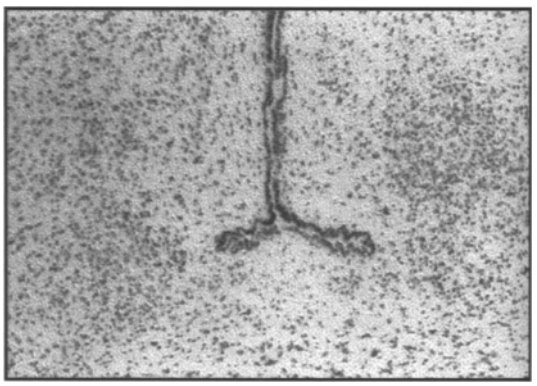

Figure 2. Microphotograph of a coronal section from the hypothalamus of a 5 days newborn capuchin monkey. The central structure is the third ventricle. The 2 zones of higher neuronal density located at both sides of the third ventricle are the SCN (magnification 40x).

Table 1. Fetal Age (as Fraction of Gestation) or Postnatal Age (Days, Years) When Components of the SCN are Detected

Species	*SCN Present*	*Neuron Number*	*AVP*$^+$	*VIP*$^+$	*Mt*	*RHT*	~
Rat	0.61	0.90	0.95	0.90	0.82	4 days	0.90
Human	0.43	1.5 years	0.73	0.73	0.43	0.80	NA
Other primates	0.31	NA	NA	NA	NA	0.70	0.70
Sheep	0.40	0.68	NA	0.62	NA	0.40	0.68

NOTE. Other primates: data from baboon, rhesus, and squirrel monkeys. SCN detected by histology.[9,11,12,60] Neuron number: completion of definitive (adult) number of neurons.[9,11,12] AVP$^+$ and VIP$^+$: neurons detected by immunohistochemistry.[9,13,14] Abbreviations: Mt, melatonin binding sites[15,16]; RHT, innervation by the retinohypothalamic tract[9,18]; ~, day/night oscillation in metabolic activity or c-Fos[9,61,62]; NA, information not available.

present in the fetal SCN.[5] Postnatal development of neurons containing AVP and VIP has been studied in the rat and in humans.[9,12,13,15] In both, the number of neurons containing these peptides increases postnatally; in humans the number of neurons present in the adult SCN is attained by 2 years of age.[12,15] No data in fetal SCN neuron number or neuropeptide content is available for nonhuman primates. Receptors for potentially entraining signals are present in the fetal SCN. The human fetal SCN and the rat SCN have binding sites for melatonin, whereas D1 dopamine receptors are present in the SCN of fetal rats and newborn baboons.[15-17] The adult pattern of innervation of the SCN by the RHT is attained during gestation in sheep and nonhuman primates.[11-18] In humans, the RHT is present at 80% of gestation or earlier.[18] In contrast, the innervation of the SCN by the RHT occurs after birth in the rat. Further stages of SCN development, such as establishment of synapses between SCN neurons, glial proliferation, and connections to other hypothalamic regions, have only been studied in rodents and take place after birth.[9,19] Despite the differences just reviewed, fetal SCN neurons from rats, nonhuman primates and sheep display a day/night rhythm of metabolic activity that, as in the newborn (Fig 3) and the adult, is higher at noon than at midnight, indicating entrainment of the fetal SCN neurons to the L:D cycle. Altogether, the evidence available suggests that during fetal life, the circadian system is "immature" (by adult standards). However, as stated by Davis[10] "it must be considered that entrainment of a circadian pacemaker in the fetus is of functional significance and is not present simply as the initial expression of a mechanism that has function in the postnatal animal only."

Circadian Rhythms in the Fetus and Newborn

A way to address the previous consideration is to investigate whether the function of the pacemaker over circadian rhythms is present in fetal life. Human, monkey, and sheep fetuses show 24-hour rhythms in hormones, behavior, and cardiovascular function (reviewed in ref 5). In

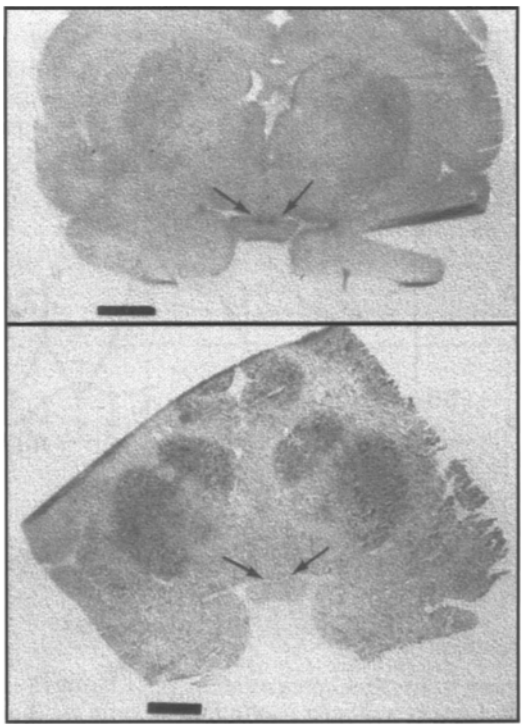

Figure 3. Metabolic activity of the *Cebus apella* SCN at 5 days of age. Autoradiographic printings of brain coronal sections containing the SCN from a newborn injected with 2-deoxy-D-glucose-1-^{14}C at noon (upper panel) and another newborn injected at midnight (lower panel). Arrows indicate the SCN. Bar: 0·5 cm.

sheep fetuses, circadian rhythms of AVP in cerebrospinal fluid and plasma prolactin (PRL) are present.[20-22] Both rhythms are entrained to the L:D cycle, as fetuses of different ewes are no longer synchronized when the ewes are kept in continuos light.[20-23] The observation that the rhythm of fetal plasma PRL disappears when the fetal hypothalamus is injured supports fetal control of this rhythm.[24] No such data are available for any rhythms in human or nonhuman primates.

An additional approach is to investigate whether rhythms are present in cord blood and in preterm and term newborns. In the term human fetus, a rhythm of cortisol is detected in samples obtained from the umbilical artery, but not in those from the umbilical vein (Fig 4), indicating a 24-hour rhythm in cortisol production by the fetus.[25] This is consistent with the observation of a rhythm in estriol in maternal plasma in women and of adrenal steroids in the fetal rhesus monkey.[26,27] The presence of a rhythm of cortisol in cord blood, in which a single sample is obtained from each newborn, implies that all newborns were tuned to the same

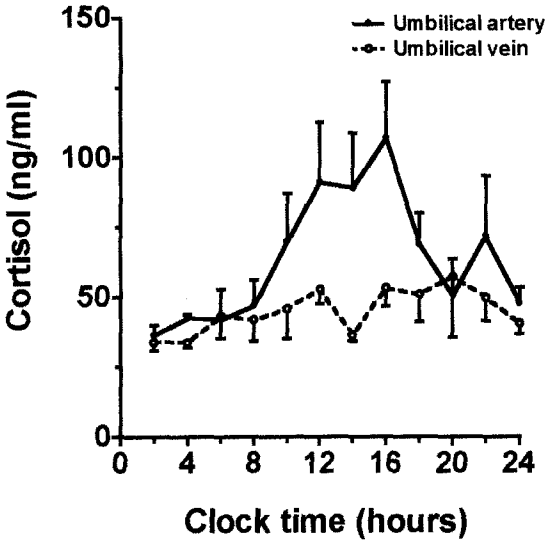

Figure 4. Cortisol concentration in 24 hours in umbilical artery and vein in the human term newborn. Cord blood samples were obtained from 60 newborns delivered by elective histerotomy due to obstetrical reasons. Surgeries were scheduled at 2 hours intervals. Each data point represents the mean of 3 to 7 newborns. A significant A-V difference in cortisol concentration was present between 1200 and 1600 hours. (Reprinted and modified with permission.[25]).

environmental cue. Rhythms in fetal breathing movements (FBM), fetal limb movements, and fetal heart rate are detected in the human fetus since midgestation.[28-30] The fetal heart rate and fetal limb movements rhythms were absent in the fetus of an adrenalectomized pregnant women.[31] These rhythms disappear on suppression of normal maternal (and fetal adrenal function) with triamcinolone and reappear when the treatment ends, suggesting dependence upon the maternal cortisol rhythm.[32] In sheep, the maternal pineal hormone melatonin may be required for the FBM rhythm, as fetuses of pinealectomized ewes show no rhythm, whereas maternal infusion of melatonin mimicking the nighttime pattern of this hormone re-established the rhythm. In addition, maternal melatonin may be able to entrain the FBM rhythm, since shifting of the time of the melatonin infusion resulted in a shift of the fetal rhythm.[33]

In human newborns, the ontogeny of the rhythms of temperature, cortisol, and melatonin have been extensively studied. Characterization of a rhythm requires frequent measurements from the same individual, ideally performed over several days. With this paradigm, Mirmiran et al[34] detected a rhythm of body temperature in 7 out of 12 preterm newborns at 29 to 34 weeks postconceptional age, maintained in an incubator at constant temperature and fed orogastrically every 2 hours. Lighting in the neonatal intensive care unit (NICU) was on continuously. Five of these newborns also showed a rhythm of heart rate (in the remaining two the record was not adequate for analysis). Analysis of the data by Chi-square periodogram revealed periods ranging from 24 to 27 hours and variability of period length from one day to the other in any given newborn. Another finding of this study was that phases of the rhythms were not synchronized with time of day. Studies in healthy full-term newborns at 2 days and 4 weeks of age show the presence of a circadian rhythm of rectal and skin temperature in all newborn studied, and of heart rate and systolic blood pressure in about half of them.[35] Examination of the acrophases of these rhythms in individual neonates at these 2 ages show a tendency to clustering in a shorter daytime segment at 4 weeks of age than at 2 days. Amplitude of the circadian temperature rhythm increased with age as also shown in other reports.[36,37] Measurements of cortisol in plasma, in

saliva, and in urine collected at fixed intervals have been used by several investigators to assess the presence and development of a circadian rhythm of cortisol in preterm and term newborns and in older infants.[38-44] Overall, available data show that the adult type of cortisol rhythm, with higher values in the morning than in the evening, is established 2 to 4 months after birth in infants irrespective of whether birth occurred at term or preterm. Nevertheless, a circadian rhythm differing from the one found in the adult may be present at an earlier postnatal age, as suggested by the detection of nonsynchronized 24-hour changes in the concentration of cortisol in urine of sick and healthy preterm and term newborns, and in saliva in some healthy preterm and term neonates.[41, 43, 44] A daily rhythm of plasma melatonin with higher concentrations at nighttime hours is present in adult mammals.[45,46] The development of the melatonin rhythm in human newborns has been studied extensively by Kennaway's group by measuring the excretion of the metabolite 6-sulphatoxymelatonin (αMT.6S) in urine.[47] In contrast to the evidence discussed for the rhythms of temperature and cortisol, the emergence of the rhythm of melatonin is tied to postconceptional age instead of postnatal age. An important factor is the limited synthesis of melatonin by the newborn pineal gland.[47-49] A circadian rhythm of αMT.6S, with an increased excretion at night, is established by 48 to 52 weeks of postconceptional age.[47] Factors experienced in utero affect the pattern of increase of melatonin excretion at night and thus total melatonin excretion in 24 hours. Infants born preterm after premature rupture of membranes, preeclampsia, intrauterine growth retardation or fetal distress, excreted less αMT.6S at 49 to 52 postconceptional weeks than infants born at term, and than infants born preterm after spontaneous labor.[50] An intriguing observation is that some of these prenatal conditions may have long-term consequences upon melatonin production, as small size at birth is associated with low αMT.6S excretion in adults.[51]

These data suggest that synchronized circadian rhythms are present in the human fetus. Some of them (heart rate, cortisol) are also detected in the newborn. A rhythm of temperature is detected in preterm and term newborns, while the rhythm of melatonin is clearly a postnatal developmental event. The observation that fetal rhythms are synchronized with the external light cycle, whereas the same rhythms in newborns are not, suggests the loss of an entraining signal at birth.

Signals Entraining the Clock in the Fetus and Newborn

In rats and hamsters, it has been well established that the mother provides time clues that entrain the fetal SCN. Maternal signals "set" the phase of the fetal SCN[52]; the SCN phase remains fixed after birth. The innervation of the SCN by the RHT (that in the rat occurs postnatally) then allows pups to entrain directly to the L:D cycle (Fig 5). Entrainment of the fetal SCN requires an intact maternal SCN.[53] In the absence of the maternal SCN, melatonin, dopamine agonists and timing of food availability, entrain the fetal clock and therefore the rhythms expressed in the newborn.[54] It is possible that these first 2 signals interact, as maternal pinealectomy increases melatonin and D1 receptors in the fetal and newborn rat SCN.[16] In primates, melatonin and dopamine agonists are also good candidates as entraining signals for the fetal SCN. Melatonin binding sites are present in the human fetal SCN and dopamine D1 receptors in the baboon SCN.[15,17] Preliminary evidence shows the expression of melatonin receptors in the hypothalamus of the capuchin monkey.[55] Presently, we are

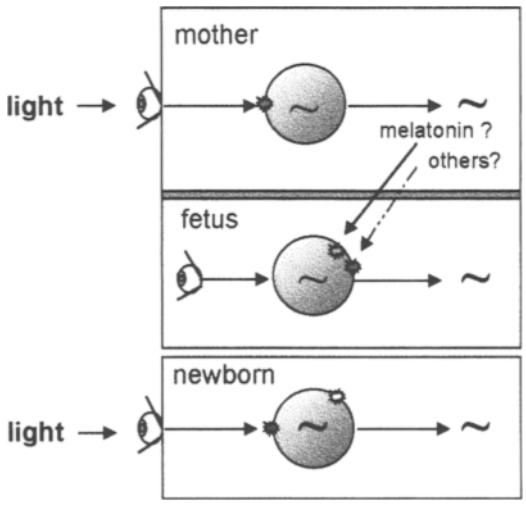

Figure 5. Schematic representation of the time keeping system in the fetus and in the newborn.

studying the effect of suppressing maternal melatonin upon the 24-hour rhythms in the newborn. Our preliminary results suggest that keeping pregnant monkeys in constant light suppresses maternal melatonin and that alters the phase of the rhythms of cortisol and temperature in the newborn (Forcelledo et al, unpublished data, 2001; Fig 6).

Concluding Remarks

The human fetus is far from living in a timeless environment. Even delivery itself is a circadian event, as most deliveries are timed to the early morning hours.[5] Maternal circadian rhythms of activity/rest, eating/fasting, temperature, heart rate, blood pressure, cortisol, melatonin, pregnancy hormones as estriol, estradiol, and progesterone impinge on the fetus. Additionally, in the last weeks of gestation, the fetus is rocked by a circadian rhythm of uterine activity.[56,57] No longer in the fetal milieu, the neonate moves to an environment in which the main time giving signal is the L:D cycle. Teleologically, a term neonate should be fit to face this challenge. But the situation may be quite different for a preterm infant that trades the circadian environment to which it was previously exposed for the timeless environment of the NICU. Several researchers have suggested that provision of an L:D cycle in the NICU may be valuable for the neonate.[4,36,37,51,58]. The SCN should respond to L:D once the RHT innervation is established. Experimental evidence in preterm baboons at an age equivalent to a 24 weeks' gestation human infant, show a response to light stimulation.[18] Supporting a response to exposure to L:D, infants born after premature rupture of membrane fitted with eye patches every night excreted more αMT.6S nocturnally at 52 weeks postconceptional age than those that remained in the lit nursery or in a dim light nursery. No effect was observed on growth.[50] However, positive effects of exposure to a L:D cycle are suggested by a randomized trial in healthy preterm newborns that showed larger weight gain after discharge from the hospital.[59] Given the absence of an effective management of circadian rhytmicity in the timeless environment of the NICU, it is important that scientist and physicians seek new experimental and clinical approaches to answer the challenging questions of perinatal chronomedicine. Moreover, we have yet to learn what potential effects in fetal/neonatal circadian rhythms may derive from use of hormonal treatments, ie, antenatal corticosteroids, dopamine, during the perinatal period.

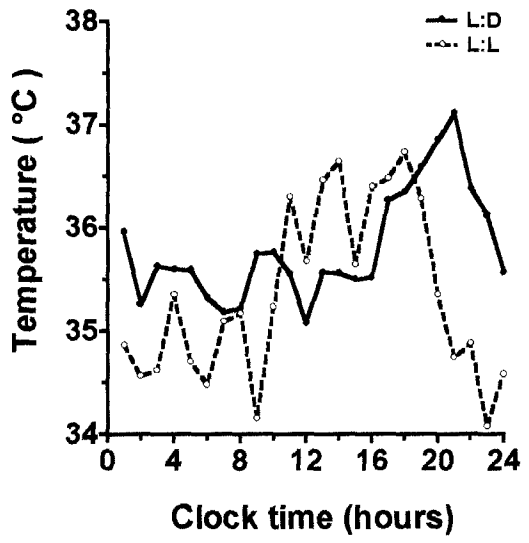

Figure 6. Twenty-four-hour changes in body temperature in two 4-day-old capuchin monkeys. Data were collected by radiotelemetry at 15-minute intervals over 24 hours. Newborns were the product of term pregnancies. Continuos line: control newborn whose mother was kept in L:D conditions during pregnancy. Broken line: newborn whose mother was maintained in continuous light (L.L) from 60 % gestation.

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