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REVIEW

ONTOGENETIC DEVELOPMENT OF THE MAMMALIAN CIRCADIAN SYSTEM

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This review summarizes the current knowledge about the ontogenetic development of the circadian system in mammals. The developmental changes of overt rhythms are discussed, although the main focus of the review is the underlying neuronal and molecular mechanisms. In addition, the review describes ontogenetic development, not only as a process of morpho-functional maturation. The need of repeated adaptations and readaptations due to changing developmental stage and environmental conditions is also considered. The review analyzes mainly rodent data, obtained from the literature and from the author's own studies. Results from other species, including humans, are presented to demonstrate common features and species-dependent differences. The review first describes the development of the suprachiasmatic nuclei as the central pacemaker system and shows that intrinsic circadian rhythms are already generated in the mammalian fetus. As in adult organisms, the period length is different from 24 h and needs continuous correction by environmental periodicities, or zeitgebers. The investigation of the ontogenetic development of the mechanisms of entrainment reveals that, at prenatal and early postnatal stages, non-photic cues deriving from the mother are effective. Light-dark entrainment develops later. At a certain age, both photic and non-photic zeitgebers may act in parallel, even though the respective time information is 12 h out of phase. That leads to a temporary internal desynchronization. Because rhythmic information needs to be transferred to effector organs, the corresponding neural and humoral signalling pathways are also briefly described. Finally, to be able to transform a rhythmic signal into an overt rhythm, the corresponding effector organs must be functionally mature. As many of these organs are able to generate their own intrinsic rhythms, another aspect of the review is dedicated to the development of peripheral oscillators and mechanisms of their entrainment. The latter includes control by the central pacemaker as well as by distinct environmental signals. Ecological aspects of the described developmental changes in the circadian system and some practical consequences are also briefly discussed.

Keywords Ontogenesis, Circadian rhythms, Rodents, Humans, SCN, Peripheral oscillators, Molecular clockwork, Photic entrainment, Non-photic entrainment, Internal coupling

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INTRODUCTION

The circadian system undergoes dramatic changes during life, particularly during early ontogenetic development and in old age (Davis, 1981; Gubin and Weinert, 1991; Mirmiran et al., 1992; Weinert, 2000). During the developmental stage, processes of maturation and adaptation to the environment take place. As a result, all biological processes show reproducible and stable high-amplitude circadian rhythms of characteristic phasing with respect to other biological processes and the external environment. A considerable number of investigations have been dedicated to changes in the circadian system during ontogenetic development. One reason for this is the obvious practical relevance of such studies to humans. Such investigations are of theoretical interest also; from the study of the development of circadian rhythms, one can draw conclusions about the role of the various components of the circadian system. This in turn allows an optimization of environmental conditions to guarantee optimal ontogenetic development (Brandon et al., 2002; Kennaway, 2002; Rivkees, 2004; Schimmel et al., 2002; Waterhouse et al., 2000; Weinert et al., 1994).

The research on ontogenetic changes of circadian rhythm mirrors the developmental progress in chronobiological research, and one may separate several stages. Early investigations were aimed at evaluating the endogenous, hereditary nature of circadian rhythms. The findings of these studies showed that circadian rhythms may develop under constant environmental conditions, depending mainly on the maturity of the organism. Efforts were undertaken to define general rules of the ontogenetic changes in rhythm characters, like range, phase, or period length (Hellbruegge, 1960; Petren and Sollberger, 1967; Rensing, 1965). The effect of environmental factors was investigated subsequently. This was done not only to clarify their role as zeitgebers but also their relevance in modifying or imprinting the development of the circadian system (Davis, 1981). With the discovery of the suprachiasmatic nuclei (SCN) as the central pacemaker of the circadian system in the early 1970s (Weaver, 1998), research was focused on the development of clock mechanisms. Now it was possible not only to study overt rhythms, *i.e.*, the hands of the clock, but intrinsic rhythms of the clock itself. Investigation explored the developmental stages at which the SCN started to show rhythmicity and when they were entrainable by photic or non-photic cues. A most important step was the discovery of clock genes and of the molecular machinery that generates circadian rhythms (Albrecht, 2004; Young and Kay, 2001), allowing the analysis of clock function and its development more directly. Finally, when it was shown that clock genes are expressed in all the cells of an organism and that several oscillators exist in brain regions other than the SCN as well as the periphery (Abe et al., 2001b; Balsalobre, 2002; Schibler and Sassone-Corsi, 2002), the view of the

circadian system of mammals had to be revised. It is widely accepted now that the circadian system of mammals comprises a web of oscillators, with the SCN at the center (Reppert and Weaver, 2002; Sakamoto et al., 1998). An important discovery was that different oscillators can be entrained by different photic or non-photic zeitgebers, that may lead to an uncoupling (Damiola et al., 2000; Stokkan et al., 2001). These recent findings will lead to a new wave of ontogenetic studies.

Investigation of the development of circadian rhythmicity must consider several aspects. The first is the development of oscillators and the establishment of intrinsic rhythms. Another concerns the development of entraining pathways allowing synchronization to the periodic environment. The third is maturation of effector systems. Finally, the development of internal coupling between oscillators and effector organs has to be investigated.

The aim of this review is to summarize the current knowledge about the ontogenetic changes in the circadian system and to encourage researchers to revisit former results, taking into account recent chronobiologic discoveries. Changes of the overt rhythms are described, and the putative underlying mechanisms are analyzed. In accordance with the traditional concept that circadian rhythms are controlled by a central pacemaker which in turn is entrained by the periodic environment, this review first describes the development of this pacemaker and the mechanisms of its entrainment. With the recognition that effector organs may generate their own rhythms, a separate part of the review is dedicated to the development of peripheral oscillators and mechanisms of their entrainment, including their control by the central pacemaker and by distinct environmental signals. Ecological aspects, such as changes in the adaptative capability of organisms and changes in the environment over the course of development plus their possible consequences in terms of the biological fitness of the individual also are briefly discussed. The review analyzes mainly rodent data derived from the literature and the author's own studies. Relevant findings from other species, including humans, are presented to show the general validity of the ontogenetic changes described, as well as special species-specific features.

DEVELOPMENTAL APPEARANCE OF OVERT CIRCADIAN RHYTHMS

Overt circadian rhythms occur at different postnatal ages, as shown in the following examples from studies on laboratory rats. It has been shown that the basal level of corticosterone undergoes daily changes from postnatal day 22 (P22); whereas, the stress corticosterone levels reveals such changes only after P26 (Levin and Levine, 1975). An activity rhythm is found by P9/10 (Smith and Anderson, 1984) and day-night change of

body temperature even earlier, in the first week after birth (Nuesslein and Schmidt, 1990; Spiers, 1988). Also in humans, different circadian rhythms develop at different ages (Hellbruegge et al., 1964; Rivkees, 2003; Sitka et al., 1994; Weinert et al., 1994). As in rodents, the appearance of overt rhythms does not depend on the duration of time that neonates live under a periodic environment, but instead on developmental stage. The corresponding organ/function must mature. This becomes particularly obvious when comparing full and preterm newborns (Sitka et al., 1993). This does not mean, however, that environmental periodicities lack influence on the development of circadian rhythmicity (Brandon et al., 2002; Rivkees, 2004). Also, particularly from human studies, it is obvious that in investigating the development of overt circadian rhythms one must distinguish between endogenous clock- and exogenously-driven (*e.g.*, lifestyle), components (Weinert et al., 1997).

Whereas most studies demonstrate the appearance of overt rhythms postnatally, evidence suggests that a circadian pacemaker might function before rhythms are overtly expressed. When pups are born and raised in continuous darkness or constant light, they develop circadian rhythms, the phasing of which resembles that of their mothers. When pups are reared by a foster mother with a different rhythmic pattern from that of their original mother, the rhythmic phase of the pups is closer to that of the original mother, suggesting that the original mother plays the predominant role in setting the pups' rhythm (Deguchi, 1975; Hiroshige et al., 1982; Honma et al., 1984a). These findings suggest that a circadian clock is oscillating at or before birth and that its phase is coordinated with and by the mother.

In large mammals, including humans, overt circadian rhythms are demonstrable prenatally. Thus, daily rhythms of hormone concentrations are found in fetal sheep (Leake et al., 1986; McMillen and Nowak, 1989b). In human fetuses, 24 h rhythmic changes are known for activity (gross movement), breathing, and heart rate (Arduini et al., 1986; de Vries et al., 1987; Patrick et al., 1980; Visser et al., 1982). That the fetal biological clock is able to generate circadian rhythms becomes evident also from studies on pre-term neonates. Body temperature rhythms are evident during the first days of life, even though the babies are deprived of maternal entrainment and are kept under constant environmental conditions in the neonatal intensive care unit (Mirmiran et al., 1992; Sitka et al., 1984; Sitka et al., 1993; Weinert et al., 1990).

DEVELOPMENT OF THE SUPRACHIASMATIC NUCLEI AS THE CENTRAL PACEMAKER

Circadian rhythmicity in mammals is controlled by the SCN, which is composed of a bilateral pair of structures located in the anterior

hypothalamus, immediately dorsal to the optic chiasm. It generates self-sustained oscillations and controls peripheral rhythms by means of neural and humoral signalling pathways. In the adult animal, the SCN has two anatomically and functionally distinct subdivisions. A ventrolateral division, the core, comprises primary neurons that produce vasoactive intestinal polypeptide (VIP) or gastrin-releasing peptide (GRP). It lies adjacent to the optic chiasm and is the target of the retinohypothalamic and the geniculohypothalamic tracts, the main afferents transferring the photic zeitgeber information from the retina to the SCN (see below). A dorsomedial division, the shell, surrounds the core and is characterized by a population of arginin vasopressin (AVP)-containing neurons (Moore et al., 2002; Moore and Silver, 1998).

The SCN as an Oscillator

Most of the work on the development of the mammalian SCN has been done on rats (Moore, 1991). The available data indicate that the rat is an appropriate model for other mammals, though differences in the duration of the prenatal period must be considered. In rats, the prenatal period lasts 22 to 23 days; in mice, 19 to 21 days; and in the Golden hamster, 16 days (Wolfensohn and Lloyd, 1998). The SCN of rats is formed from embryonic day 14 (E14) through E17 from a specialized zone of the ventral diencephalic germinal epithelium as a component of the periventricular cell groups. Neurons making up the shell are generated first (on E15/E16) followed by those of the core (on E16/E17). The neurogenesis ceases by day E18, although a gradual maturation of neuronal morphology can be observed until postnatal day 10 (P10). Synaptogenesis in the SCN is mainly a postnatal process. At E19, there are only a very few synapses. Their number increases until P10, when the synaptic density achieves the adult level.

Intrinsic SCN rhythmicity is already present in the late embryonic stage. In rat fetuses, Reppert and Schwartz (1983) demonstrated a circadian oscillation of metabolic activity by monitoring the uptake of C14-labeled deoxyglucose. The rhythm is detected as early as embryonic day 19, that means 2 to 3 days before birth (Reppert and Schwartz, 1984b). At that time, SCN neurogenesis has only just finished (see above). In vitro studies confirm that the circadian rhythm of metabolic activity in fetal SCN is really an intrinsic one (Shibata and Moore, 1988). A day-night oscillation of vasopressin mRNA levels is evident on embryonic day 21 (Reppert and Uhl, 1987), indicating a regulated expression of the vasopressin gene already during fetal life. The firing rate of SCN neurons starts to exhibit a clear circadian rhythm on embryonic day 22 (Shibata and Moore, 1987), *i.e.*, largely prior to the formation of synaptic contacts within the SCN (Moore, 1991). The firing rate gradually increases

from E22 to P14, with emergence of patterns of firing of individual neurons that approximate those of the adult SCN.

Also in primates, an endogenous circadian pacemaker seems to be functional late in fetal development. Using the 14C-labeled deoxyglucose method, a daily pattern of glucose utilization in the suprachiasmatic nuclei was shown (Reppert and Schwartz, 1984a). In humans, several rhythms, which are driven by the SCN in adults, are present prenatally. Rest-activity, breathing movements, heart rate, and urine production show circadian patterns in the fetus as reviewed in depth elsewhere (Mirmiran et al., 1992). There is some evidence that these rhythms are controlled by the fetal SCN. In humans, the SCN are formed by week 18 of gestation and already possess melatonin receptors (Reppert et al., 1988); thus, they may generate self-sustained and entrainable oscillations (see also below). That rhythms obtained *in utero* are not a direct consequence of maternal rhythmicity is supported by studies revealing phase differences between mother and fetus (Arduini et al., 1986; Leake et al., 1986; McMillen et al., 1987).

The clock mechanism that generates the daily rhythms is considered to involve interacting transcriptional/translational feedback loops based on rhythmic expression of the mRNA and proteins of clock components (Albrecht, 2004; Reppert and Weaver, 2002). Eight mammalian, mostly mouse (m), clock genes cloned so far (three period genes: *mPer1, mPer2, mPer3*; two cryptochrome genes: *mCry1, mCry2; Clock, Bmal1*, and *casein kinase 1 epsilon*) are thought to be involved. Briefly, the clock genes *Period* and *Cryptochrome* are switched on by the proteins Clock and Bmal, and are periodically switched off by a complex of their own encoded proteins, Per and Cry.

Sládek et al. (Sladek et al., 2004) investigated the pre- and postnatal development of the molecular clockwork in the rat SCN. Circadian profiles of five clock gene mRNAs, namely of *Per1, Per2, Cry1, Bmal1*, and *Clock*, were studied on embryonic day 19 (E19) and postnatal days 3 (P3) and 10 (P10). Embryonic day 19 was chosen because neurogenesis in the fetal SCN is completed by this time (Moore, 1991). Also, a circadian rhythm in metabolic activity is already present (Reppert and Schwartz, 1984b). All studied clock genes are expressed in the SCN at E19, although no circadian rhythm is detectable in their expression. In addition to putative strain differences, one reason may be that the SCN rhythmicity just begins at this embryonic stage (Fuchs and Moore, 1980; Reppert and Schwartz, 1984b), and therefore the amplitude of the rhythms in clock gene expression might be too low to be detected. Also, rhythms in clock gene expression might be present in individual SCN neurons but the neurons might not be sufficiently synchronized because of the very low number of synapses found on E19 (Moore, 1991). Early in the postnatal period, at P3, significant rhythms in *Per1, Per2, Cry1*, and *Bmal1*

mRNA, but not in *Clock* mRNA, are expressed in the SCN, and these rhythms mature gradually. On P10, the amplitude is more pronounced than on P3 (Sladek et al., 2004).

Ohta and colleagues (2002, 2003) recently reported on rhythms of Per1 and Per2 mRNA in the fetal rat SCN already by E20. Also in mice, the measurement of clock gene expression in fetal SCN reveals intrinsic prenatal rhythms. A daily rhythm of *Per1* mRNA is detected already at E17, and this might reflect the somewhat shorter embryonic period of mice. However, the rhythm of *Per2* expression is not present even on P3, and it appears only on P6 (Shimomura et al., 2001).

As already mentioned, one cannot completely exclude the possibility that fetal rhythms are driven by the mother. However, the literature shows that the elements constituting the molecular clock are present by the late embryonic stage and that rhythmic gene expression is at least inducible. A more detailed analysis of the molecular clockwork development should include not only clock gene expression and concentrations of their protein products, but also the development of post-translational modulation and intracellular translocation of these products (Yagita et al., 2000, 2002).

Entrainment of the SCN

The available evidence indicates that a biological clock oscillates in the mammalian SCN, beginning from the late embryonic stage. However, such a clock would generate a rhythm slightly different from 24 h, as it has been shown very clearly in adult organisms. Therefore, a continual correction by environmental periodicities, or zeitgebers, is necessary. In mammals, this is realized mainly by the light-dark cycle. However, in the early developmental stages, terminal embryonic span, and initial postnatal days, non-photic cues seem to be more effective.

Non-Photic Entrainment of the Fetus

The fetal clock is supposed to be entrained by the mother's time cues, *i.e.*, the environmental lighting acts through the maternal circadian system, as shown in experiments on rats and golden hamsters. When mothers are blinded, the rhythm of fetal SCN metabolic activity is synchronized with the free-running rhythm of their mothers (Reppert and Schwartz, 1983). The dams need to have an intact SCN, as demonstrated by experiments in which the maternal SCN is destroyed early in gestation (Reppert and Schwartz, 1986b; Davis and Gorski, 1988; Honma et al., 1984a; Honma et al., 1984b; Shibata and Moore, 1988; Weaver and Reppert, 1989b). However, the maternal SCN have only an entraining function and do not generate the fetal rhythms, as shown by

analyzing glucose utilization in individual brains (Shibata and Moore, 1988). When the data of different, non-synchronized pups are pooled, as is done in most studies, circadian differences are attenuated. Also, the drinking behavior of pups born and raised by SCN-lesioned dams shows circadian rhythmicity, although the phases of different individuals are distributed randomly over the 24 h period (Weaver and Reppert, 1989b). Taken together, these results show that in individual animals a rhythm may persist, but with desynchronization within the litter. The results also provide evidence that, in these early developmental stages, synchronization can be realized only by the mother and not by interactions between the siblings.

Davis and Gorski (1988) investigated the wheel running activity of golden hamsters born to and reared by SCN-lesioned mothers under constant conditions. As with the drinking behavior in rats (see above), the phases of the activity rhythms are scattered throughout the 24 h, indicating lack of synchronization. The authors also provided evidence that maternal SCN lesions on embryonic day 10 disrupts synchronization, whereas lesions on day 12 do not. This result suggests that, after neurogenesis, the setting of phase in the fetal SCN occurs in the hamster between E10 and E12 (Crossland and Uchwat, 1982). In other words, prenatal entrainment begins approximately at the time as SCN neurogenesis is completed.

Honma et al. (1984a; 1984b) provided evidence that, in rats, maternal-fetal coordination of circadian phase may occur before day 10 of gestation—long before the SCN is formed. These conclusions are based on phase differences of the corticosterone rhythm, suggesting an alternative interpretation that instead of the SCN an adrenal clock has been set. The adrenal glands develop at very early embryonic stages (Abrin, 1969).

Nature of the entraining signal for the fetus is still under debate, as the fetus is exposed to a multitude of maternal rhythms—behavioral, metabolic, hormonal, cardio-vascular, *etc*. Earlier studies focused on hormones, the prime candidate being melatonin. As it can cross the placenta, melatonin may communicate phase information to the fetus (McMillen and Nowak, 1989a; Reppert et al., 1979; Yellon and Longo, 1987). However, maternal pinealectomy does not abolish maternal coordination of fetal circadian rhythms. Also, extirpations of other maternal endocrine organs such as pituitary, adrenals, thyroid-parathyroids, or ovaries (each performed in separate experiments) does not abolish maternal coordination of metabolic activity in the fetal SCN (Reppert and Schwartz, 1986a).

On the other hand, timed injections of pharmacological doses of melatonin into SCN-lesioned golden hamsters restores fetal synchrony (Davis and Mannion, 1988). Also, neonatal hamsters can be entrained by melatonin injections. This effect disappears, however, after P6 (Grosse

et al., 1996). Presumably, melatonin directly acts on the fetal SCN, which is known to express melatonin receptors (Duncan and Davis, 1993; Reppert et al., 1988; Weaver et al., 1988). Experiments with SCN grafts confirm the hypothesis that fetal SCN contains an entrainable oscillator, which is directly sensitive to melatonin, though only during a certain stage of development. Rhythmicity of SCN-lesioned Syrian hamsters is restored by transplanting fetal SCN. Daily injections of melatonin do entrain the rest-activity rhythm; however, injections given 6 weeks after transplantation no longer are able to entrain rhythms (Grosse and Davis, 1998).

The dopaminergic system is also implicated in maternal-fetal entrainment. Periodic treatment of SCN-lesioned dams with the D_1-dopamine receptor agonist SKF38393 is capable of entraining fetuses and early postnatal rats (Grosse and Davis, 1999; Viswanathan et al., 1994; Weaver and Reppert, 1995). As with melatonin, dopaminergic cues might directly act on the SCN which are known to express D_1-receptor mRNA (Viswanathan et al., 1994; Weaver et al., 1992). Moreover, treatment with cocaine or D_1-receptor agonist induces the expression of *c-fos* within the fetal rodent SCN (Bender et al., 1997; Viswanathan et al., 1994; Weaver et al., 1992). Studies on adult rodents show the expression of immediate-early genes, like *c-fos, junB*, and *egr*-1, in the SCN is correlated with photic phase resetting of the circadian clock as reviewed elsewhere (Hastings et al., 1995; Rea, 1998). Thus, the induction of *c-fos* following D_1-receptor activation may also be associated with a clock-resetting event. In the early post-natal period, the entraining effect of D_1-receptor stimulation and its ability to stimulate IEG expression is lost, for example, in the Syrian hamster by P6 (Grosse and Davis, 1999).

Melatonin and dopaminergic cues entrain the fetal clock to opposite phases, regardless of when the compound is given (Viswanathan and Davis, 1997). Melatonin might be viewed as a dusk or nocturnal cue and dopamine as a diurnal cue. *In vivo*, it is likely that both signal pathways operate in a complementary and possibly redundant way, defining subjective night and day.

In primates, the endogenous circadian pacemaker, as measured by the 14C-labeled deoxyglucose method, is coordinated with ambient lighting via the maternal circadian system during the late fetal period (Reppert and Schwartz, 1984a). Preliminary results on a primate (*Cebus paella*) suggest that maternal melatonin may play a role in synchronizing the perinatal circadian system to environmental signals (Seron-Ferre et al., 2002). Also in humans, the circadian clock seems to be entrainable. The SCN possess melatonin receptors, both in the adult and fetal stage, indicating that the influence of melatonin on human circadian rhythmicity may begin *in utero* (Reppert et al., 1988). Because melatonin receptors occur in both central and peripheral tissue, the influence of melatonin

on the developing human fetus may not be limited to entraining the central pacemaker (Thomas et al., 1998). Dopaminergic agents may also influence the primate circadian system. Recent studies reveal mRNA and functional D_1-receptor within the fetal and adult primate SCN, including that of humans (Rivkees and Lachowicz, 1997).

Experiments with restricted food access revealed that rhythmic food ingestion can also entrain fetuses of SCN-lesioned rats (Weaver and Reppert, 1989b). Several mechanisms might be involved. Rhythmic food ingestion causes rhythmic fluctuations of nutrients or metabolites in the blood and generates rhythms of motor activity or body temperature. All these signals have been shown to be capable of entraining circadian oscillators (Brown et al., 2002; Rutter et al., 2002; Sakamoto and Ishida, 2000; Stokkan et al., 2001). The available literature data suggest there is not a single entraining signal, but that several maternal rhythms act in concert to entrain the fetal biological clock.

Non-Photic Entrainment of the Neonate

In altricial rodents (like mice, rats, and hamsters), the maternal circadian system continues to coordinate the timing of the pups during the postnatal period. The magnitude of maternal influence is most apparent during the first days of life until the pups start to leave the nest, to forage, and to eat on their own. In precocious rodents, on the other hand, a robust maternal-fetal communication can be observed but no postnatal maternal influence. These species, *e.g.*, guinea pigs or spiny mice, are born at a developmental stage allowing an autonomous life. The main entraining signal (zeitgeber) for them is the light-dark cycle (see below).

That maternal cues exert a powerful effect on the neonatal clock of altricial rodents has been shown by cross-fostering studies. Newborn litters entrain to the circadian phase of their foster mother if fostered within the first weeks of life (Duffield and Ebling, 1998; Hiroshige et al., 1982; Honma et al., 1987; Reppert et al., 1984; Takahashi and Deguchi, 1983). Also, 24 h cycles of maternal presence and absence have a synchronizing effect on rat pups (Shimoda et al., 1986; Sugishita et al., 1993) and newborn mice (Viswanathan, 1999; Viswanathan and Chandrashekaran, 1985). The onset of activity of the pups coincides with the beginning of the period of the mother's absence.

Under natural conditions, the pups are probably never directly exposed to environmental day-night cycles. The mother helps the pups to maintain or reinforce the timing of the outside world until they are ready to begin independent lives. Importantly, the mother keeps her normal, nocturnal activity pattern. She stays inside the burrows, making contact with the pups during the day and foraging at night. Even under

laboratory conditions, the dams are active and do not have contact with the pups during the actual or subjective night time (Viswanathan, 1999). Figure 1 illustrates this for laboratory mice. The mother mouse keeps her normal activity pattern with most activity during the dark span. Thus, she is present in the nest during the light and absent during the

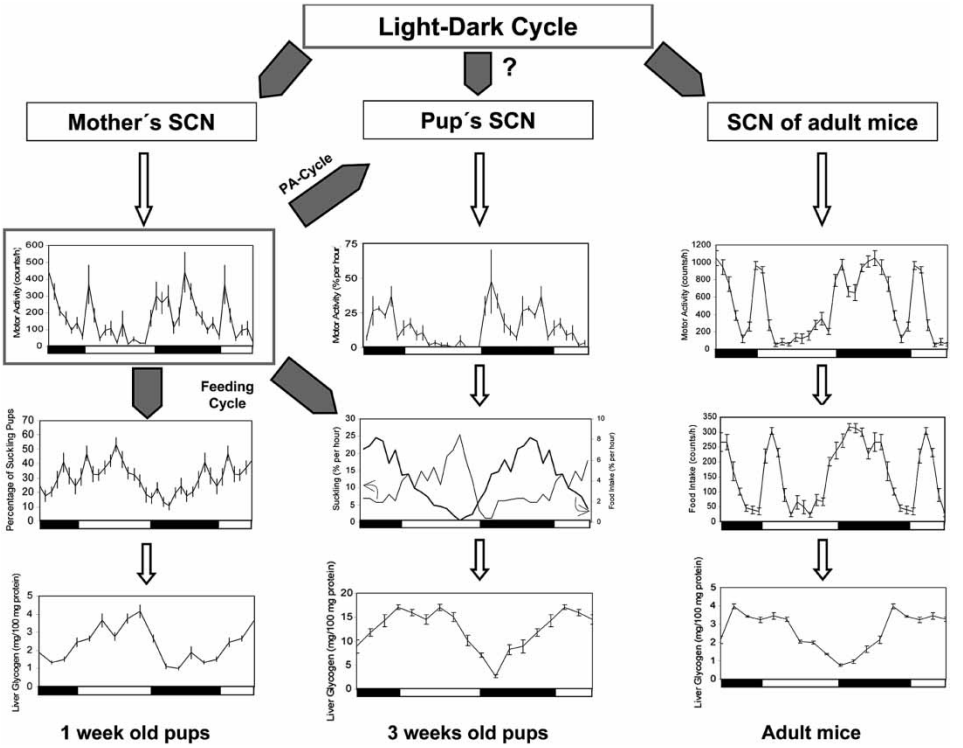

FIGURE 1 Photic and non-photic entrainment of mice at different ages. The light-dark cycle entrains the SCN of adult mice, including mothers. A photic synchronization of pre-weanling mice is possible, although under natural conditions, they are probably not directly exposed to environmental lighting. Mother mice are synchronized with the periodic environment and keep their normal activity pattern (upper left panel). As it is typical for adult mice (upper right panel), they are mainly active during the dark span and feed their siblings predominantly during the rest span. As a consequence, the 1-week-old pups show a feeding pattern with a maximum during the light span (middle panel, left), that is about 12 h out of phase as compared to the feeding pattern of adult animals (middle panel, right). Accordingly, the daily rhythm of liver glycogen shows a nearly opposite phase position in young mice (lower left panel) as compared to adult animals (lower panel, right). In addition to the feeding cycle, mother mice impose a presence-absence (PA) cycle on the siblings. This acts directly on the SCN of the pups and entrains them to a similar phase as it is typical for adult animals. The motor activity (upper panel in the middle) and the feeding pattern (middle panel in the middle, bold line) achieve their maximum during the dark span. Even though pups at an age of 2 to 3 weeks leave their nest to forage, they are still fed also by their mothers during the light span (middle panel in the middle, thin line). As a consequence of these two opposite feeding patterns, the glycogen rhythm (lower panel, middle) has an intermediate phase position. The activity and feeding patterns of 3-week-old mice were obtained by videotracking. The other patterns are redrawn from our earlier publications (Weinert and Schuh, 1984a; Weinert and Schuh, 1984b; Weinert and Schuh, 1988).

dark span. In addition to this presence-absence cycle, she produces a feeding cycle. Feeding of the pups occurs mainly during the light span. As a result, the pups show a rhythm of food intake (suckling) that is nearly inverse in phasing as that of adult mice (Weinert and Schuh, 1984a). A similar phenomenon occurs in rats (Ader and Grota, 1970; Levin and Stern, 1975; Redman and Sweney, 1976; Walker et al., 1974).

It remains to be established what constitutes the time cue for maternal entrainment, as well as what constitutes the molecular mechanism that underlies the entrainment. Importantly, social contact between the mother and pups during the 12 h presence of the mother is taken by the pup to be the subjective day and 12 h absence of the mother is taken by the pup to be the subjective night (Viswanathan, 1999). Pups engage in numerous activities with the mother, which involve primarily cutaneous contact. They remain cuddled together in the nest and huddle (contact behavior) closely with one another. This huddling is dominated by olfactory and thermotactile cues (Alberts and Brunjes, 1978). Altricial mammals subsist entirely on mother's milk (Thiels et al., 1990), and it is well known that lactating female rats and mice produce chemical cues or pheromones that attract their altricial pups for suckling (Leon, 1975; Porter and Doane, 1976). Absence of the nursing mother, on the other hand, is stressful for neonates, and involves both psychological and physiological stressors such as cold, starvation, dehydration and a lack of passive maternal contact. Maternal absence alters the responsiveness of the neonatal hypothalamus–pituitary–adrenal (HPA) axis to external stimuli (Dent et al., 2000a, 2000b; Meaney, 2001). All these factors either alone or in combination, may be mediating the pups' entrainment during the presence/absence cycles of the mother.

The neural pathways responsible for synchronization by behavioral contact between mother and offspring are not known, although they may be similar to those involved in arousal-induced entrainment in the adult (Hastings et al., 1998). However, there is an important difference as the potency of maternal entrainment declines with maturation of the pup's circadian system (Reppert et al., 1984; Shimoda et al., 1986; Viswanathan, 1999).

At the level of the molecular clockwork, current models of resetting the adult SCN by behavioral cues focus on the down-regulated expression of both Per1 and Per2 (Maywood et al., 1999), whereas photic resetting is accompanied by their upregulation (see below). Recently, two studies from Honma's group were published measuring rPer1 and rPer2 expression in the SCN to answer the question of whether maternal rhythm affects pup circadian pacemakers. Newborn rats were blinded and reared by foster mothers under normal or inverted light-dark cycles. Slight, but significant, differences in the circadian rhythms of rPer1 and rPer2 were observed between the two groups of rats

(Ohta et al., 2002), suggesting an involvement of the molecular clock in the neonatal SCN. At the same time, these findings showed that the influence of the nursing mother was weak. A second study therefore focused on maternal absence rather than on maternal care (Ohta et al., 2003). Maternal deprivation during the light time phase reversed the circadian rhythms of rPer1 and rPer2 mRNA in the neonatal SCN, while cross-fostering phase-shifted the Per expression rhythms in the SCN only by ~2 h (Ohta et al., 2002). Taking the results of both studies into consideration indicates that absence of the mother, rather than maternal care, seems to play the critical role in entrainment.

As shown by Honma's group, periodic absence of the mother during the hours of nursing phase-resets the neonatal circadian clock. Also, it results in phase reversal of behavioral rhythms measured after weaning (Ohta et al., 2003). This is the first evidence for entrainment of the molecular clock in the SCN by time cues other than light. In adult rodents, non-photic time cues significantly alter the phases of the behavioral rhythms, but they do not affect the circadian expression of the clock genes in the SCN at all (Damiola et al., 2000; Hara et al., 2001; Wakamatsu et al., 2001). Also, stress does not seem to affect the molecular clock in the SCN of adult rodents (Takahashi et al., 2001). These findings suggest that the sensitivity of neonatal SCN to non-photic time cues differs from that of the adult SCN.

Photic Entrainment

The only receptor for photic information is the retina (Freedman et al., 1999; Morin, 1994). Besides rods and cones, other retinal photoreceptors are involved in circadian entrainment, namely retinal ganglion cells containing melanopsin (Berson et al., 2002; Menaker, 2003; Rollag et al., 2003; Brown and Robinson, 2004). The information reaches the SCN mainly via a direct projection, the retino-hypothalamic tract, and, to a lesser extent, also by other pathways, especially by the geniculo-hypothalamic tract (Moore et al., 2002; Rea, 1998).

In the rat, retinal ganglion cell axons leave the retina and form the optic nerve on E15. The optic chiasm and the primary optic tract are formed on E16 and E17. The retinohypothalamic tract (RHT) appears to form as collaterals of primary optic tract axons within the optic chiasm. At early developmental stages (E18-P1), the optic chiasm and the SCN are clearly separated by a distinct border. On P2, axons from the chiasm begin to enter the ventral SCN, and a very active synaptogenesis in the ventral part of the SCN can be observed between P4 and P10. The density of innervation gradually increases and reaches the adult pattern on P15. Through this same period, NPY-containing axons of geniculate origin establish synaptic contact (Moore, 1991; Speh and Moore, 1993).

Different approaches are used to establish the developmental appearance of light responsiveness of the circadian system. The metabolic activity of the SCN, as estimated by the 2-deoxyglucose-method, is reported to increase following light exposure at night beginning on the day of birth (Fuchs and Moore, 1980). Other approaches did use the effect of light exposure on the pineal N-acetyltransferase (NAT) activity, a key enzyme of melatonin production. The circadian rhythm of NAT activity is controlled by the SCN and first appears on PD3. The inhibition of enzyme activity by light exposure at night is first observed on PD6 (Bronstein et al., 1990; Vanecek and Illnerova, 1985). At the same time, direct light-dark entrainment is detected (Duncan et al., 1986) Juvenile rats of different age were exposed to phase-shifts in the light-dark cycle and the pineal N-acetyltransferase rhythm was monitored. The results show that retina-mediated, light-dark entrainment begins by postnatal day 6 and overrides maternal entrainment by postnatal day 8.

The light/dark information, perceived by photopigments in the eye and transferred via neuronal connections to the SCN, induces gene expression, thus entraining the SCN to the light/dark schedule. Following a light pulse, Ca^{2+}-dependent kinases are activated and subsequently mitogen-activated protein (MAP) kinases and the transcription factor CREB (calcium/cAMP response element binding protein) (Ginty et al., 1993; Obrietan et al., 1998). These acute responses are followed by induction of mRNAs from several genes, including *c-fos* (Hastings et al., 1995; Rea, 1998) and *Period*, a core element of the SCN clockwork (Field et al., 2000; Shigeyoshi et al., 1997). Importantly, light exposure increases the expression of these genes only during the subjective night, when it also phase-shifts circadian rhythmicity (Colwell and Foster, 1992; Kornhauser et al., 1990; Rusak et al., 1990). The changes in gene expression in the SCN are believed to be the critical mechanism of resetting the adult SCN clockwork. Current models focus on upregulated expression of both Per1 and Per2 (Albrecht et al., 2001; Field et al., 2000; Shigeyoshi et al., 1997). The activation of CREB probably plays a central role in this process. It appears rapidly in the SCN following a light pulse and drives the expression of IEG's and Per genes via CRE sequences in their respective promoters (Best et al., 1999; Ginty et al., 1993; Obrietan et al., 1999; Field et al., 2000).

Taking into account this knowledge, a more sensitive approach to investigate the developmental appearance of light-dark entrainment seems to be the assessment of light-induced *c-fos* gene expression in the SCN. It is a more direct estimate of the photic input and can be obtained in individual animals. Photic induction of *c-fos* has been shown to occur in even earlier ontogenetic stages if compared with approaches described above. In the rat, it is found on the day of birth (Weaver and Reppert, 1995) or the day after (Leard et al., 1994). In Syrian as well as in Siberian

hamsters, light increases Fos-like immunoreactivity beginning from P3 (Duffield et al., 1995; Kaufman and Menaker, 1994). In mice, light-induced Fos-like protein in the SCN occurs first on P4 (Munoz et al., 2000). The obtained small differences between species may be caused by temporal differences in the formation of photic afferents. For example, the RHT starts to innervate the SCN in the Syrian hamster some days later than in the rat (Speh and Moore, 1993).

In adult animals, light-induced *c-fos* expression is restricted to a certain circadian time ("gate"), namely the subjective night, when light pulses also cause phase shifts of circadian rhythmicity. Thus, the circadian "gating" is a prerequisite of light-dark entrainment. Weaver and Reppert (Weaver and Reppert, 1995) obtained it in rats first on P2. In another study (Bendova et al., 2004), light exposure at any time of the day induced high c-Fos production in the SCN of 3-day-old rat pups, whereas at 10 days of age a circadian "gating" was present.

The literature indicates that retinal input can activate cells in the SCN very early in post-natal life. Pups of altricial animals are able to perceive light even before the eyelids open, though light appears to be a less potent entraining signal than maternal cues. At a certain time, both zeitgebers are active in parallel, though providing conflicting time information as they are in antiphase (Figure 1). As a consequence, the pups show a diurnal pattern of suckling and a nocturnal pattern of food and water intake. In precocious species, which are born at an advanced stage as compared to altricial species like rats and hamsters, the light entraining neural pathways are developed before birth. Weaver and Reppert (Weaver and Reppert, 1989a) demonstrated that in the spiny mouse (*Acomys cahirinus*) the retinohypothalamic tract is present and functioning on the day of birth. A direct perception of environmental lighting is observed in fetal spiny mice already late in gestation, although it is a less potent entraining agent than maternal cues at this developmental stage. After birth, the LD cycle is the main zeitgeber.

Rhythmic Output Signals

In order to function as a circadian pacemaker, the SCN needs to transfer the rhythmic information to various targets, especially to effector organs. This can be achieved by neural connections via the autonomous nervous system and/or by diffusible/humoral messages.

Efferent projections from the SCN to various areas of the hypothalamus and to other central brain structures control several body functions and are part of the circadian system (Bartness et al., 2001; Kalsbeek and Buijs, 2002). Little is known about their ontogenetic development. Some efferent projections appear to be present by day P4 (Moore, 1991). In addition to neural projections, diffusible factors transfer

information from the SCN to other brain regions (LeSauter and Silver, 1998; Kalsbeek and Buijs, 2002; Silver et al., 1996). Two neuropeptides, transforming growth factor-α (TGF-α) and prokineticin-2 (PK2), have recently been identified as candidate output factors (Cheng et al., 2002; Kramer et al., 2003). The developmental appearance of these humoral signalling pathways remains to be investigated.

A more indirect way of controlling the phase of peripheral oscillators is to entrain them by regulating the rest/activity cycle or the timing of feeding behavior. Thus, a zeitgeber for the lung or the heart might be alteration in locomotor activity (Sakamoto and Ishida, 2000; Stokkan et al., 2001). Both organs are more active when animals are exercising; in other words, the pacemakers are set to match the time of the organs' optimal activity with the time of maximal physical exertion. Also, rhythmic food intake could exert an entraining influence more broadly, probably via metabolites (see below). Brown and coworkers (2002) investigated the effect of temperature cycles *in vitro* on circadian gene expression. The prerequisite for all these signalling pathways is the establishment of stable, overt rhythms.

MATURATION OF EFFECTOR ORGANS PERIPHERAL OSCILLATORS

To be able to transform a rhythmic signal from the central pacemaker system, the corresponding effector organs or systems must mature functionally. Thus, the appearance of the daily rhythm of motor activity only after postnatal days 9 to 10 seems to be due to insufficient physical abilities rather than to a lack of rhythmic signals. Another good example is the circadian rhythm of body temperature. It appears in rats during the first postnatal week. However, torpor-like temperature falls occurred incidentally, as a consequence of an immature thermoregulatory system (Nuesslein and Schmidt, 1990).

Investigation of the functional development of different organs or physiological regulatory systems is beyond the realm of the current review. Concerning effector systems, another aspect should be discussed, however. Many, if not all, peripheral organs are able to generate their own intrinsic rhythms. Therefore, the corresponding functions are not as much driven by the SCN as entrained by them (Reppert and Weaver, 2002). Whereas many investigations have been performed on the SCN, a detailed analysis of peripheral oscillators has only just started.

Clock genes are widely expressed in other brain regions such as the cerebral cortex, the hippocampus, areas rich in neuroendocrine cells (Abe et al., 2001a; b; Dudley et al., 2003; Kriegsfeld et al., 2003; Mrosovsky et al., 2001; Wakamatsu et al., 2001), and in various peripheral organs including the liver, heart, lung, and muscle (Balsalobre

et al., 1998; Balsalobre, 2002; Damiola et al., 2000; King et al., 1997; Sakamoto et al., 1998; Stokkan et al., 2001; Yamazaki et al., 2000; Zylka et al., 1998). As mRNA and protein products of clock components are not only present in various tissues outside the SCN but also show circadian expression, the question arises whether every cell has the potential to be a circadian clock. At least several organs produce their own intrinsic rhythms.

Whereas the cyclic expression of clock genes in the rat SCN begins early between E19 and P3 (Sladek et al., 2004; Ohta et al., 2002; Ohta et al., 2003), in peripheral oscillators this seems to happen later. A recent study on the ontogeny of circadian rhythmicity in the rat heart shows that the rhythmic expression of *Per1* and *Bmal1* starts between P2 and P5. *Per2* mRNA does not show rhythmicity until P14 (Sakamoto et al., 2002). This might be one reason for the relatively late appearance of an overt circadian rhythm of heart rate (Weinert et al., 1994). In the cerebral cortex, the daily rhythm of mPer1 and mPer2 expression appears during postnatal days P14 to P50, and this is also later than in the SCN (Shimomura et al., 2001). It seems likely that the ontogenetic development of clock mechanisms occurs independently in different organs. The most important factor, probably, is the functional maturity.

In adult organisms, peripheral oscillators are controlled by the central pacemaker, the SCN. The periodic environment, particularly the light-dark cycle, has probably only an indirect entraining influence via changes in activity or feeding schedule (Reppert and Weaver, 2002). Food, for example, is a very potent zeitgeber for the liver circadian cycle. A restricted feeding schedule almost immediately resets the phase of circadian gene expression in the liver (Damiola et al., 2000; Stokkan et al., 2001). Importantly, the phase change induced by restricted feeding in the liver is due to entrainment rather than masking, as it is maintained in fasting animals (Stokkan et al., 2001).

Providing rats and mice with food only at times when they are normally inactive entrains both locomotor activity and rhythms of clock gene expression in peripheral organs, such as the liver; whereas, it has little or no effect on the SCN (Damiola et al., 2000; Hara et al., 2001; Stokkan et al., 2001). Even when the light/dark cycle is removed as a zeitgeber, the rhythm of gene expression in the SCN is unaffected by restricted feeding. Thus, non-photic stimuli, such as a forced feeding schedule for example, can dominate light in entraining behavioral and peripheral rhythms. As the SCN remains locked on to the light/dark cycle, circadian rhythms of peripheral gene expression and behavior can be completely uncoupled from the SCN.

Newborn rats and mice are fed by their mothers predominantly during the daytime. As a consequence the pups have a diurnal type of food intake (see Figure 1). Interestingly, the daily rhythm of liver glycogen

concentration peaks in the middle of the dark time and therefore appears about 8 h later than in adult mice as estimated by Cosinor analysis. The feeding cycle imposed by the mother can be considered as some kind of time-restricted feeding, thus being a zeitgeber for the liver in a manner described above. When the pups start to move around and to forage, they show a nocturnal type of activity, obviously driven by the SCN (Figure 1). The SCN of pups seems to be synchronized via presence-absence cycles of the mother and possibly by the LD cycle, depending on the environmental conditions—laboratory or natural. Also food and water, except mother's milk, are consumed preferably during the dark span. Suckling occurs further during the light span. As a consequence, two eating patterns, which are about 12 h out of phase, are observed. The daily rhythm of liver glycogen has an intermediate phase position between the patterns of 1-week-old siblings and adult mice.

In the hearts of rat pups, a phase shift in the rhythms of clock-gene expression is observed between P14 and P20 (Sakamoto et al., 2002). It seems likely to be an inversion and occurs at the time of big physiological and behavioral changes—when the pups leave the nest, start to search for food, and decrease the amount of breast feeding. It is known from studies on human newborns that feeding can influence the daily rhythm of heart rate (Weinert et al., 1997). The study on rats provides evidence that feeding might not only be a masking factor but also a synchronizer, at least in the circadian range. During the first days of postnatal life, the heart rate rhythm may be synchronized by the feeding cycle; later it is coupled to motor activity rhythm.

Further studies are necessary to show that an imposed feeding cycle really synchronizes and not masks peripheral rhythms. Existing evidence strongly suggests, however, that during the preweanling period two zeitgebers function. One synchronizes the SCN to a phase similar to that of adult animals. Another synchronizes a food-entrainable oscillator to a phase being different by about 12 h. As a consequence, part of behavioral and physiological functions is coupled to the eating rhythm, while another part is coupled to the motor activity rhythm. After weaning, those rhythms that were synchronized by mother's feeding cycle exhibit a delaying phase shift by about 12 h, requiring several weeks to establish adult age phase positions (Weinert et al., 1987; Weinert and Schuh, 1984a; Weinert and Schuh, 1984b; Weinert and Schuh, 1988).

CONCLUSIONS

Summarizing, one may conclude that the ontogenetic development of the circadian system appears to involve processes of maturation as well as adaptation. A biological clock oscillates already in the mammalian fetus. However, the environmental conditions, including 24 h periodicities

change during life. The fetal clock is entrained by redundant circadian signals from the mother, who also entrains circadian rhythms during the initial postnatal days. This way, mothers help the developing mammal prepare for life in the outside world, outside the uterus and outside the burrows. After birth, not only are the maternal cues that entrain pups different from those during fetal life, but also the LD cycle becomes increasingly important. After weaning, the LD cycle is the main zeitgeber and the mother loses her ability to synchronize.

As a consequence of the changing environmental periodicities (different kinds of zeitgebers of varying strength), the internal temporal order, especially the phase relations between various rhythms, can change. According to the traditional view, such an "internal desynchronization" should have consequences for the health and welfare as well as physical and mental performance of the animals. However, such reorganizations in animal behavior—switches from a diurnal to a nocturnal activity pattern or *vice versa*—seem to be rather normal and may occur under various natural conditions (Mrosovsky, 2003; Weinert, 2004). These phenomena reflect the high flexibility of the timing system, necessary to adapt to environmental changes and to cope with several demands.

Another point of practical interest concerns the impact of exogenous factors. In rats, the lighting conditions during pregnancy and lactation may affect the development of the circadian pacemaker and the light-entraining system (Cambras et al., 1997; Canal-Corretger et al., 2000; Canal-Corretger et al., 2003; Malorni and Oliverio, 1978). A critical period of sensitivity to light is found between P10 and P20 (Canal-Corretger et al., 2001). In experiments done in the author's laboratory, effects on the ontogenetic development of the circadian system were found in mice kept under an inverted lighting regimen or time-restricted food conditions for 10 weeks following weaning (Weinert et al., 1989; Weinert et al., 1992). These were detectable even in adult mice, kept for several weeks under normal lighting and *ad libitum* feeding conditions. The adaptation to light-dark shifts and to time restricted feeding was different depending on the environmental conditions after weaning (Weinert et al., 1993).

In humans, the development of the fetal SCN is found to depend on the mother's lifestyle (Ferguson et al., 2000; Kennaway, 2002). The impact of cycled lighting or maternal care on the development of circadian rhythmicity in newborns has also repeatedly been shown (Ferber et al., 2002; Peirano et al., 2003; Rivkees, 2003; Waterhouse et al., 2000; Weinert et al., 1997). This is of particular relevance for preterm infants, as they are reared in the mostly "timeless" environment of a neonatal intensive care nursery (Brandon et al., 2002; Rivkees, 2004; Schimmel et al., 2002).

Altogether, these results imply that the ontogenetic development of the circadian system can be modified or imprinted by changing environmental conditions. A better knowledge of the underlying mechanisms and the critical developmental stages may help to optimize environmental conditions.

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