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Minireview

Setting the biological time in central and peripheral clocks during ontogenesis

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Abstract In mammals, the principal circadian clock within the suprachiasmatic nucleus (SCN) entrains the phase of clocks in numerous peripheral tissues and controls the rhythmicity in various body functions. During ontogenesis, the molecular mechanism responsible for generating circadian rhythmicity develops gradually from the prenatal to the postnatal period. In the beginning, the maternal signals set the phase of the newly developing fetal and early postnatal clocks, whereas the external light–dark cycle starts to entrain the clocks only later. This minireview discusses the complexity of signaling pathways from mothers and the outside world to the fetal and newborn animals' circadian clocks.

Keywords: Circadian system; Suprachiasmatic nucleus; Peripheral circadian clocks; Ontogenesis

1. Introduction

Organisms are exposed to environmental changes that recur mostly in 24-h cycles as a consequence of the Earth's rotation. The most prominent changes are cycles in light and darkness. In response to such changes, organisms evolved an endogenous clock, i.e., a mechanism that enables them to anticipate rhythmically occurring events. Even under constant environmental conditions, the clock generates rhythmic signals in about 24-h cycles and is, therefore, called circadian (from Latin circa diem). Under natural conditions, the circadian clock is entrained to the 24-h day by external cyclically occurring events, mainly by the light period of the day. Due to the entrainment, periods of rest and activity and of many other physiological functions are restricted to a certain time of the day to ensure the best strategy for obtaining food, exposure to optimal outside temperature, protection against predators and excess of sun light, etc.

In mammals, the principal circadian clock resides in cells grouped in two suprachiasmatic nuclei (SCN) of the hypothalamus [1]. In rodents, the paired nuclei are composed of about 20 000 neurons. These neurons are themselves circadian oscillators and are mutually synchronized [2]. Morphologically and functionally, the rodent SCN is divided into at least two parts, namely the ventrolateral (VL) part called the core and the dorsomedial (DM) part called the shell. The VL part receives the photic information from the retina (see below) and expresses mostly light dependent rhythms, e.g., in photoinduction of the immediate early genes (IEGs) *c-fos* and *junB* [3]. The DM part exhibits spontaneous oscillations of many rhythmic variables, like expression of the *arginine vasopressin* and *c-fos* genes [4,5]. Apart from the SCN, nearly every tissue of the body, e.g., liver, kidneys, heart, muscle, spleen, etc., contains a peripheral clock driving local rhythms specific for the tissue function [for review see 6]. Under entrained conditions, the phase of the peripheral clocks is set by the SCN program. However, the peripheral clocks rhythmicity persists even in tissue culture and may not depend on the SCN [7].

The basic molecular core clock mechanism responsible for generation of the rhythmicity within the SCN and peripheral rhythmic cells is formed by interactive transcriptional–translational feedback loops between the clock genes, namely two *Per* (*Per1,2*), two *Cry* (*Cry1,2*), *Clock*, *Bmal1*, *Rev-erbα* and *casein kinase 1 epsilon* (*CK1ε*), and their protein products PER1,2, CRY1,2, CLOCK, BMAL1, REV-ERBα, CK1ε [for review see 8]. Briefly, CLOCK and BMAL1 as a heterodimer positively activates the rhythmic expression of *Per*, *Cry* and *Rev-erbα* genes. In the cytoplasm, the PER and CRY proteins form a complex important for nuclear translocation of both proteins. After shuttling into the nucleus, the PER:CRY complex directly interacts with the CLOCK:BMAL1 heterodimer and inhibits CLOCK:BMAL1 mediated transcription. Regulation of *Bmal1* transcription is mediated mostly by REV-ERBα. The SCN and peripheral clocks operate with similar components and share a similar molecular core clock mechanism. However, some tissue-dependent differences may exist [9]. Also, phasing of clock gene expression differs between the SCN and various peripheral tissues. Peripheral clocks may be phase delayed relative to the SCN by 3–9 h. Although the molecular basis of the circadian clock has been partially defined, the molecular clock outputs that ultimately control circadian rhythms at cellular, organ and system-level are still poorly understood. Components of the core clock mechanism within the SCN and peripheral tissues may serve as down-

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stream transcription factors. At a certain time of day, they switch on transcription of a great array of tissue specific clock controlled genes that are relevant to distinct functions of these organs [10,11]. For example, about 10% of the liver transcriptome is under circadian control [12,11]. In the SCN, the arginine vasopressin (AVP) gene is one of the best-recognized clock controlled genes: it is expressed in a circadian manner and appears to augment SCN excitability [13].

2. Setting the biological clocks

2.1. Entrainment of the central clock

The phase of the central clock is set mostly by photic stimuli: exposure of animals to light in the first part of the subjective night phase-delays and in the second half phase-advances the clock [14]. The photic information is transferred from the retina to the SCN via the monosynaptic retinohypothalamic (RHT) and polysynaptic geniculohypothalamic (GHT) tracts. Besides the classical retinal photoreceptors cones and rods, a small subset of retinal ganglion cells containing the opsin-like protein melanopsin is also photosensitive and projects to the SCN [for review see 15]. The RHT and GHT terminate on a subset of retino-recipient cells in the VL SCN. The spontaneously rhythmic cells in the DM SCN receive photic information only through the VL part. In the late day, the signal of darkness may be neuropeptide Y, the main neurotransmitter of the GHT [16]. During the night, release of the RHT neurotransmitter glutamate signals "light" to the clock [for review see 17]. Light-induced clock resetting may involve sequential activation of glutamatergic NMDA and non-NMDA receptors. Depending on the time when light impinges on the retina at night, the SCN signals downstream of glutamate may diverge. In the early night, signal transduction leads to activation of ryanodine receptors and release of Ca^{2+}. In the late night, the activated cGMP-dependent pathway downstream of glutamate involves Ca^{2+} influx, nitric oxide synthetase and intracellular movement of nitric oxide. Nitric oxide can activate soluble guanylylcyclase, which increases cGMP and activates cGMP-dependent protein kinase (PKG) [18]. Activation of the second messenger pathways is followed by activation of transcription factors. The Ca_i^{2+}/cAMP response element binding protein (CREB) is phosphorylated [19] and IEGs, namely *c-fos* and *jun-B* [3] and clock genes *Per1* and *Per2* [20] are transcriptionally activated, mostly in the VL SCN. Light induced P-CREB may directly regulate transcription of *Per* genes via a CRE element in the 5′-flanking regions of their promoters [21]. Importantly, light may induce CREB phosphorylation and transcription of IEGs and clock genes only during the interval when light entrains the clock, i.e., during the subjective night [19,3]. While the role of IEGs in photic entrainment has not yet been solved, induction of *Per1* and *Per2* genes is believed to be involved in resetting the core clock molecular mechanism. Via the above-mentioned pathways, the clock may attain a new phase in response to a photic stimulus experienced at night. Also, a long day length, i.e., a long photoperiod, such as during summer days, may modulate the SCN rhythmicity as well as its molecular clockwork [for review see 17,22].

Non-photic stimuli, like enforced locomotor activity, arousal, serotonergic drugs, melatonin, dark pulses, etc., are also supposed to reset the central clock when administered at a critical time of the day, e.g., in the late day [for review see 23]. Due to the complexity of the stimuli, their resetting pathways may vary. These may, however, converge at the same endpoint since it has been demonstrated that several non-photic cues acutely downregulate the *Per1* and *Per2* genes, i.e., act opposite to light stimuli. Hence, the *Per* genes may represent the molecular target for the modulating effect of non-photic stimuli on light signaling to the clock.

2.2. Entrainment of peripheral clocks

Peripheral clocks are indirectly entrained by light via setting their phase by the light entrainable SCN clock. However, they may also be directly entrained by changes in their local environment. Under normal conditions, the indirect and direct pathways act in concert. The SCN-controlled rhythm in spontaneous feeding represents one of the strongest entraining cues for many peripheral clocks. In nocturnal animals, the feeding rhythm is related to another SCN-controlled rhythm, i.e., to the rhythm in locomotor activity. Both locomotor activity and feeding mostly occur during night. However, under certain circumstances, the local entraining cue might be in conflict with the SCN signaling. This may happen in the case when access to food is restricted to an unusual time of the day, i.e., to the daytime rest period. Under such restricted feeding, the rhythmic gene expression in liver, kidneys, heart, and other tissues is phase-shifted relative to that in animals fed ad libitum, whereas the phase of gene expression within the SCN does not change [24]. Under such conditions, entrainment of the peripheral clock mediated via the nutrition supply may uncouple from the SCN entrainment. Besides the feeding rhythm, the SCN may control peripheral clocks by humoral as well as neural pathways. In the liver, glucocorticoids have been proposed to play a role in setting the phase, as administration of dexamethasone acutely shifts rhythmic gene expression in the liver and induces rhythmic *Per* expression in cell cultures [25]. Neural pathways may involve the autonomic nervous system since adrenaline may control gene expression in the liver [26].

3. Ontogenesis of the biological clocks

3.1. Ontogenesis of the SCN clock

Development of the SCN clock proceeds in more stages from fetal to postnatal periods. In the rat, the SCN is formed as a component of periventricular cell groups during embryonic days (E)14 through E17. Neurogenesis is complete at E18 although morphological maturation proceeds until postnatal day (P)10. During prenatal period, the SCN neurons only form a few synapses [27]. In this respect, the fetal SCN might resemble an in vitro culture of dissociated SCN cells where connections between the individual cells are sparse or do not exist. Synaptogenesis progresses slowly around birth and then markedly increases from P4 to P10 [27].

It seems that appearance of the first significant rhythms in clock genes expression within a population of the rat SCN neurons proceeds in parallel with the SCN development. At E19, no rhythms of clock genes expression and no clock proteins PER1, PER2 and CRY1 are detectable [28]. At E20, formation of a rhythm in *Per1* expression is indicated and rhythms of *Per2*, *Cry1* and *Bmal1* only appear during the first postnatal days [29]. In another study, rhythms in *Per1* and *Per2* expression in the rat SCN have been reported at E20 [30,31]. Impor-

tantly, amplitude of the rhythms in *Per1* and *Per2* expression in rhythmic SCN cells increases with age until P10 [28] as the synaptogenesis progresses. The parallelism points to the importance of mutual communication between individual clock cells for generating a marked rhythmic signal. Interestingly, *Bmal1* is strongly expressed in the fetal SCN of rats [28] as well as of hamsters [32], while *Per1* and *Cry1* are expressed only weakly.

The rat SCN clock starts to drive output rhythms only around birth as the rhythm in *AVP* heteronuclear RNA is undetectable in the rat SCN at E20, i.e., 1–2 days before birth, but is clearly present at P1 [29]. The rhythm in *AVP* mRNA is detectable at E21 [33], whereas the rhythm in firing rate only at E22 [34]. Altogether, these data are in favor of the hypothesis that the rat is born with a rather immature SCN clock that develops further postnatally. It remains to be ascertained whether the day–night difference in the SCN metabolic activity, monitored by a 2-deoxyglucose uptake and detected as soon as at E19 [35], i.e., well before the first appearance of the rhythm in clock genes expression, represents an intrinsic SCN rhythmicity or a maternal cue driven change. Also, it is of utmost importance to reveal whether the lack of rhythmicity in clock genes expression within the fetal SCN is due to a lack of synchronization between single oscillating SCN cells. However, the undetectable levels of clock proteins throughout the circadian cycle at E19 [28] suggest rather a not yet fully developed core clockwork in the fetal SCN.

3.2. Ontogenesis of peripheral clocks

Development of peripheral clocks depends on maturation of the organ housing the clock as well as on maturation of the molecular clockwork. The first appearance of molecular oscillations might be thus highly organ- and species-specific. In the rat heart, rhythmic expression of *Per1* and *Bmal1* genes begins between P2 and P5 whereas that of *Per2* begins at P14 [36]. In the rat liver, rhythms in clock gene expression may start from P2 and develop further through P10 until P20 [28]. In the murine cerebral cortex, daily rhythms of *Per1* and *Per2* mRNA are detected from P14 [37].

4. Entrainment of developing clocks

4.1. Maternal signaling to fetal clocks

The fetal SCN clock is supposed to be entrained exclusively by cues delivered periodically by the mother. Though light under certain circumstances may reach the fetus even in the uterus [38], the photic pathways to the fetal SCN in altricial rodents are not fully developed. Therefore, non-photic maternal entrainment appears to be dominant. There is extensive evidence that primarily the maternal SCN sets the phase of the developing fetal clock. First, the rhythm in the fetal SCN metabolic activity is synchronized by the maternal SCN [39]. Second, the newly forming and appearing rhythms in clock genes expression in the very late fetal and early neonatal stages are, from the beginning, in phase with the maternal clock [29]. Moreover, although the maternal SCN does not generate fetal rhythms per se, it ensures the postnatal within litter synchrony [for review see 40]. In hamsters, the postnatal within litter synchrony is established very early during the fetal development as a maternal SCN lesion at E10 but no more at E12 abolishes

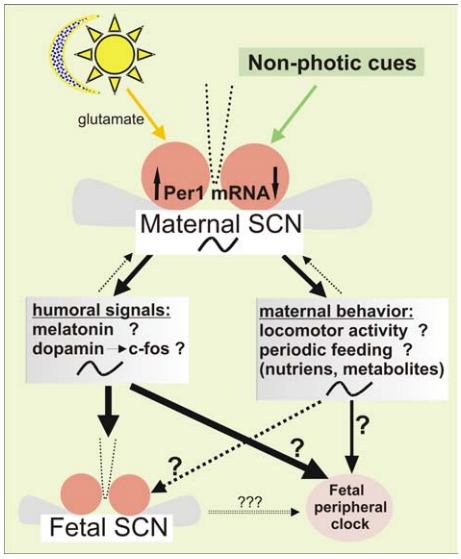

Fig. 1. Signaling to developing fetal clocks. The maternal circadian clock within the suprachiasmatic nucleus (SCN) is entrained mostly by photic and also by non-photic cues with time of the day. The underlying molecular mechanism is symbolized by Per1 mRNA that is upregulated by photic and downregulated by non-photic entraining stimuli. The entrained maternal SCN controls overt humoral and behavioral rhythms that may feedback to the maternal SCN. At the same time, the fetal SCN and perhaps peripheral clocks are entrained via as yet only partially recognized rhythmically delivered maternal stimuli. Although the fetal clocks begin to exhibit intrinsic rhythmicity of the molecular clockwork only around birth and early postnatally, the phase of the newly forming and appearing rhythms in the fetal SCN is set by the maternal SCN early prenatally. Pathways from the maternal to fetal clocks may involve signaling by dopamine via induction of c-fos and/or by melatonin (thick arrow). Also, behavioral maternal rhythms, e.g., locomotor activity and feeding may, hypothetically, entrain the fetal clocks (thin arrows). For more detail see Section 4.1.

the synchrony [41]. In rats, it is suggested that the maternal synchronization of fetal clocks occurs even before the SCN is formed [42]. If this is the case, what is the fetal anatomical substrate that is synchronized by the mother's clock? And as the molecular clockwork in the rat SCN develops mostly postnatally, what is the fetal molecular mechanism that is synchronized by maternal signals? There is also confusion concerning the photoperiodic entrainment of fetuses and newborn rodents. Djungarian hamsters maintain memory of the photoperiod experienced during their fetal stage even postnatally, i.e., the photoperiodic entrainment should be set by their mothers. However, rhythms in clock genes expression or in *c-fos* photoinduction in the neonatal rat SCN are not modulated by the photoperiod experienced by mothers during pregnancy [43,44], though photoperiod modulates the rhythms in the adult rat SCN [for review see 22]. The above-mentioned rhythms, as well as the overt rhythm in the pineal melatonin production, start to be photoperiod dependent only around P10 [for review see 40]. A question arises as to where the memory of the photoperiod experienced during the fetal stage is stored, if not in the neonatal rodent SCN?

Also the entraining signal from mother to fetus is still not completely understood. A designed candidate must exhibit a circadian variation, penetrate the placenta and act at a functional receptor or affect neuronal activity of the fetal SCN. It is difficult to imagine how the fetal clock might become en-

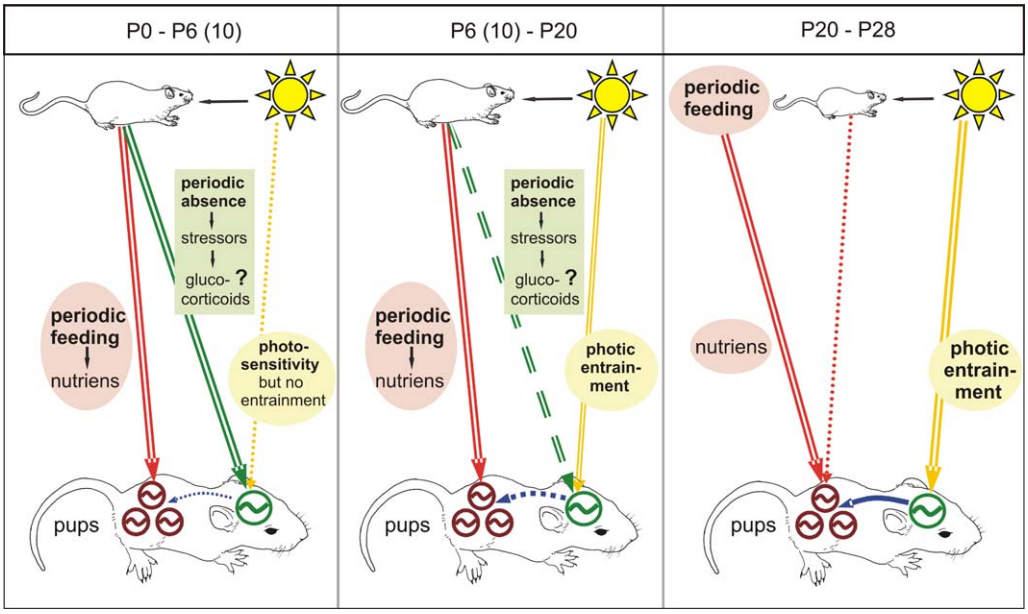

Fig. 2. Signals entraining clocks after birth. Three developmental periods in rodents are depicted: (i) about first week of life, i.e., between the postnatal day 0 and 6–10 (P0–P6(10)); (ii) since the end of the first week until P20 involving the start of weaning (P6(0)–P20); and (iii) between P20 and the end of weaning at P28 (P20–P28). P0–P6(10): During this period, pups are fully dependent on maternal care and maternal entrainment prevails. Periodic absence of the mother might entrain molecular oscillations within the pup's SCN clock via glucocorticoids. Periodic breast feeding and maternal care entrain molecular oscillations in the peripheral clocks. Although the newborn pup's SCN clock is already photosensitive, the photic entrainment does not yet occur. P6(10)–P20: during this period, pups open their eyes and start to be partially independent of their mothers. Significance of maternal absence as an entraining cue of the pup's SCN is losing and the pup's SCN clock begins to be entrained by photic stimuli. At the same time, the pup's SCN may start to control peripheral clocks. Moreover, apart from the maternal day-time feeding, pups begin gradually to forage themselves during the night-time and molecular oscillations of peripheral clocks shift accordingly. P20–P28: during this period, pups become completely independent of their mothers and maternal entrainment is lost. Similarly as in adults, the SCN clock is entrained dominantly by photic cues and peripheral clocks by nocturnal feeding regime. The SCN clock may entrain molecular oscillations in peripheral clocks either directly or rather indirectly via entraining the feeding regime with the external daytime. For more details see Sections 4.2 and 4.3.

trained before it becomes rhythmic itself. Hypothetically, the mechanism might be similar to induction of oscillations in peripheral clock cells in vitro following the addition of serum [45]. At a certain time of day, an entraining maternal cue may trigger a signaling pathway that might impinge onto the yet non-rhythmic clock cells and induce expression of certain genes. Consequently, an imprinting of time awareness might be initiated. Alternatively, a maternal signal might synchronize already existing oscillations in individual cells. Maternal melatonin may fulfill all the criteria of a functional entraining cue and was considered as a first class candidate at least for the photoperiodic entrainment. However, it appears that hormones are not exclusive entraining cues for the fetal clock. Activation of dopaminergic pathways through D1 receptors entrains rodent fetuses as well [46]. Dopamine receptors, as well as melatonin receptors, are present in fetal SCN cells [47]. While melatonin might be considered as the signal of night, dopamine might be the signal of day. The dopaminergic signaling includes activation of the IEG *c-fos* within the fetal SCN [48]. In the adult rat SCN, *c-fos* expression is spontaneously high during the daytime and low during the nighttime [5]. *c-fos* expression is likely related to neuronal activation which is also high during the day and low during the night. Importantly, a marked rhythm in cFos protein immunoreactivity in the neonatal rat SCN is present at P3, i.e., at the earliest time tested [44]. Preliminary data show that the rhythm might be present even at earlier developmental stages (El-Hennamy et al., unpublished results). It is therefore possible that maternal cue-induced *c-fos* expression may provide the fetal clock with a daytime signal and elevation of neuronal activity. It is not yet clear, however, how the suggested signals and pathways may induce rhythmic expression of clock genes. The signaling pathways activating *c-fos* and *Per* genes share a common element, i.e., phosphorylation of CREB. This step might represent the crucial point triggering rhythmic clock gene expression. As more cues share the ability to induce phosphorylation of CREB and expression of *c-fos*, the induction might, hypothetically, represent a common step setting the daytime in the fetal clock (see Fig. 1).

4.2. Signals entraining the central clock postnatally

In rodents, such as rats, mice and hamsters, the newborn neonates are fully dependent on their mothers. In the laboratory, the exquisite maternal entrainment of their rhythmicity becomes less important after the first week of their life when the photic entrainment starts to override the maternal entrainment. In nature, the switch from maternal to photic entrainment may correlate with the ability of pups to leave their underground burrows and get exposed to the environmental light. The mechanism underlying the change in sensitivity of the clock to entraining signals is not fully understood. The phase of the newborn rat SCN clock is set prenatally, synchronously with the mother's clock. Rat pups are born, however, with a low-amplitude oscillation in clock genes expression and the amplitude increases only gradually [28,29]. At the early developmental stage, pups may be partly entrained to the different circadian phase of a foster mother [for review see 40]. This maternal entrainment may be facilitated or even enabled by the low amplitude of pups' clock

oscillations. As the clock rhythmicity strengthens, maternal cues may lose the ability to entrain it and a stronger entraining agent, i.e., light, may take their place.

Maternal cues entraining the pups' clock postnatally may not be the same as those entraining the fetal clock. Many potentially entraining substrates, such as, e.g., melatonin, may be delivered in milk. Recent studies however indicate that this pathway may contribute only little to resetting the pups' clock. When blinded newborn rats are reared by a foster mother on an inverted light–dark regime, the phase of rhythms in *Per1* and *Per2* mRNAs within the pups' SCN is shifted only marginally by about 2 h [30]. Maternal behavior, namely absence of the mother, may, however, strongly entrain the neonatal clock. When newborn pups are deprived of their mothers during the light phase, i.e., at the time when they usually suckle milk, the rhythmic SCN expression of *Per1* and *Per2* genes is completely phase-reversed within six days [31]. Likely, the feeding regime and the periodic partial maternal absence are not the crucial resetting cues for the pups' SCN clock, as they are also reversed under the fostering experiment [30]. The complete absence of the mother at the time when pups are usually fed may be, however, a strong stressor for pups altering expression of stress related genes, such as *corticotropine releasing hormone*, *glucocorticoid receptor* and *AVP* [31]. Hypothetically, the signaling pathway involved in the maternal postnatal entrainment might employ glucocorticoids similarly as with entrainment of peripheral clocks in adults. Sensitivity of the SCN clock to stress diminishes with postnatal age [49].

As innervation of the VL SCN via RHT and GHT develops mostly during the first days after birth, pups become more sensitive to light and gradually the photic entrainment of the SCN clock prevails. The signaling cascade responding to light is functional at least partly immediately after birth: light pulses induce *c-fos* expression in the rat SCN on the day of birth [48] or at P1 [50]. The light induced gene expression is, however, not the only pre-requisite for photic resetting the circadian clock. The photic entrainment may be accomplished mostly due to the fact that light induces the signaling cascade only during a restricted time window that corresponds to the duration of subjective night. During the subjective night, the SCN clock is sensitive to light and photic stimuli may phase delay or phase advance the clock depending upon the time of their administration. The mechanism of how the molecular clockwork gates the response to light is still not understood. The gate for insensitivity to light is not yet developed at P3 since light pulses administered at any time within a 24-h cycle induce high cFos immunoreactivity in the SCN no matter whether it is day or night [44]. In another study [48] a slight gate was indicated at P2. However, the gate for insensitivity to light becomes present only at P10 [44]. This day corresponds well with the developmental stage when photic entrainment begins to override maternal entrainment [for review see 40]. Moreover, at P10 the rat SCN clock starts to be entrained by the photoperiod [43]. In comparison with adult rats [51], the photoperiodic control of the molecular clockwork is only partial and even at P20 it is not yet complete [43]. The data suggest that at least in rodents, the postnatal photic and photoperiodic entrainment develops in dependence on advancement of the mechanism that gates the clockwork insensitivity to light. The development proceeds gradually and may be accomplished at the end of the weaning time (see Fig. 2).

4.3. Signals entraining peripheral clocks postnatally

During postnatal ontogenesis, the circadian expression of clock genes in the rat peripheral clocks might be entrained not only by signals from the developing SCN clock, but also by maternal behavior, namely by the rhythm in breast feeding and care of the newborns. The latter possibility seems to be the case in the first weeks of life. The mother feeds her pups and thus keeps them active mostly during the day. Adult rats, however, are active and consume food mostly at night. During the weaning period, between P14 and P28, the pup's feeding and activity regimes apparently change. In parallel with the changes, the phases of rhythms in genes expression in the heart change as well [36]. First, the phases shift by several hours between P14 and P20. The shifts, though smaller, continue, together with a drastic change of the rhythm's amplitude between P20 and P30, when the matured circadian system seems to have been established. Similarly, during development of the molecular clockwork in the rat liver, rhythms of clock genes expression appear to phase shift during the first weeks of life [28]. Apparently, at this developmental stage, setting peripheral clocks by the feeding regime may prevail upon entrainment by the SCN (see Fig. 2).

5. Concluding comments

This minireview cannot encompass all known data on biological clocks and their entrainment during development. From the data summarized it is, however, obvious how little is known about biochemical signals setting the time in the clocks. Many questions still remain to be answered. What may be the pathways setting the phase of the SCN clock prenatally by the mother at the time when the fetal SCN is not yet formed or at the time when the molecular clockwork is not yet functioning? And what pathways mediate maternal entrainment of the central and peripheral clocks during the first weeks after delivery?

It is of great importance to recognize principles of maternal and photic entrainment of the circadian system during development. This system plays a significant role in controlling many physiological processes and understanding the mechanisms of its entrainment during ontogenesis might facilitate optimization of conditions necessary for its healthy development in animals, as well as human beings.

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