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Chapter 9

Circadian Rhythms in Children

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[For Springerlink]

Abstract

Circadian rhythms are generated by an endogenous circadian timing system. The biological clock, a key component of the circadian timing system, is anatomically located in the suprachiasmatic nucleus of the anterior hypothalamus and its functioning is grounded on a genetic-based negative feedback loop mechanism. Circadian rhythms are entrained to the 24-hour cycle by so-called Zeitgebers or synchronizers that can be environmental – such as the dark/light cycle -, social – e.g., school start time –, or biological – like melatonin.

One of the most widely investigated circadian rhythms is the sleep/wake cycle, the organization of which can be understood within the theoretical framework of the two-process model of sleep regulation. Looking at this model from a developmental perspective, it can be supposed that sleep (S) or the homeostatic process may be preponderant over the circadian (C) process in early life because homeostasis is an intrinsic basic function of living beings aimed at avoiding possible interference from the environment. The C process, on the contrary, is supposed to help the S process to gradually tune with environmental changes. It is probable that this is the reason why the C process undergoes a progressive development that is completed at the end of adolescence, changing the balance between the two processes, and becoming preeminent compared to the S process. After the C process completes its maturation, it starts to progressively weaken with age, leading to a new balance between the two processes.

Keywords: Circadian rhythms, children, circadian process, homeostatic process, preterm birth, chrononutrition, photoperiod at birth, individual difference, circadian preference, developmental changes

Endogenous Origin of Circadian Rhythm: The Circadian Timing System

Circadian rhythms, which present a period of around 24 hours, are endogenously generated by the circadian timing system. The circadian timing system is composed of an input pathway, the biological clock, and the output pathway. The input pathway through photoreceptors detects and transmits information from the retina to the biological clock, which is anatomically localized in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. The biological clock then transmits its outputs to other brain areas, generating circadian rhythms, which are entrained to the 24-hour cycle by so-called Zeitgebers or synchronizers. Among the environmental synchronizers, the dark/light cycle is commonly acknowledged as the most powerful for the human species. However, at different levels, other synchronizers can be detected. For example, school start time and melatonin represent examples of social and biological synchronizers, respectively.

Although in humans the fetal SCN has been recognized at an early stage (i.e., around mild gestation) [1], at gestational term it is still largely immature. The SCN undergoes an intensive development during the very first few months of postnatal life [2]. This means that at birth circadian rhythms are still not apparent; furthermore, environmental variables during early postnatal life could importantly affect the emergence and consolidation of these rhythms.

Examples of Interactions Between Circadian Timing System and the Environment

Preterm Birth

Each milestone of the development of the circadian timing system is modulated not only by biological mechanisms, but also by interaction with the environment. One example of such interaction is represented by the preterm birth. Indeed, it has been shown that preterm infants are characterized by the earlier appearance of a 24-h sleep/wake rhythm (i.e., one of

the most widely investigated circadian rhythms) compared to full-term infants (e.g., [3]). A possible explanation of this result is that the earlier and more regular exposure of preterm infants to environmental signals such as light (e.g., the cycled light conditions) [4] and social time cues (e.g., regular feeding pattern) [5] in the neonatal care unit plays a primary role in the earlier appearance of a 24-h sleep/wake rhythm. Interestingly, results from research into the relationship between preterm birth and circadian preference suggest an association between preterm birth and an early imprinting of the SCN. Although circadian preference will be presented later in the chapter, it can basically be described as a continuum with evening types (those who prefer to perform mental and physical activities later in the day, and would rather stay up late at night and wake up late in the morning) and morning types (those who show a preference toward early bedtime and get-up time, as well as to performing demanding activities in the morning) at the extremes and intermediate-types (no clear preference toward morning or evening activities) in the middle [6]. Previous studies [7, 8] have shown an association between preterm birth and morningness preference, i.e., a preference toward an early phase of the sleep/wake cycle, which could be related to an early imprinting of the SCN in preterm born children [9].

Chrononutrition

Another example of interaction with the environment that could modulate the development of the circadian timing system is represented by human milk as a potent form of chrononutrition [10], which may have been shaped by evolution in aiming to transmit information to the infants regarding the time of day. It is interesting to observe that human milk differs in its composition according to the time of day. In particular, during the daytime human milk is composed of higher levels of activity-promoting amino acids and cortisol [11], which could increase alertness. On the contrary, during the nighttime, the levels of such

activity-promoting factors decrease concurrently with an increase in the levels of melatonin [12] and tryptophan, which could improve sleep and the consolidation of sleep/wake rhythms. Since breastfeeding is not always possible, knowledge regarding chrononutrition has been applied to the development of dissociated milk formulas with daytime and nighttime components, which mimic the aforementioned circadian variations in human milk. It is interesting to observe that experimental evidence seems to point out that the administration of this dissociated formula milk helps the consolidation of the sleep/wake rhythm in infants [13, 14]. In line with these observations, the study by Cohen Engler and colleagues [15] pointed out that infants who were exclusively breastfed showed a trend toward longer nocturnal sleep duration compared to those exclusively fed with artificial formula milk that was not dissociated into daytime and nighttime components.

Photoperiod at Birth

Photoperiod at birth represents another example of an environmental factor that could interact with and modulate the development of the circadian timing system. Indeed, it is known that annual changes in daylight occurring during the early stages of development could affect the development of the SCN, the anatomical structure that is accountable for the generation and entrainment of circadian rhythms [9]. It is thus possible that a phenomenon similar to an imprinting could happen during a sensitive stage of development immediately after birth, with the first 3 months of life suggested as a critical time for the development of sleep/wake rhythm in humans [16]. An interesting study in mice showed that perinatal photoperiod has an imprinting-like effect on the mammalian circadian clock [17], with those developing in a long photoperiod (16 hours of light and 8 hours of dark) presenting shorter circadian periods compared to those perinatally exposed to a short photoperiod (8 hours of light and 16 hours of dark). Bearing in mind that mice are nocturnal animals, these data point

out that mice exposed to a long photoperiod present a phase advance of the circadian timing system while those exposed to a short photoperiod show a phase delay. Season of birth is considered a useful marker of the perinatal photoperiod, with autumn and winter associated with decreasing and short photoperiods, while being born in spring and summer is connected with increasing and long photoperiods. During the developmental age, Touchette and colleagues [18], examining mostly Caucasian children aged between 4 and 6 years, highlighted a trend in wake-up times that were delayed in those born during spring-summer compared to those born in autumn-winter. The effects of season of birth have also been investigated with reference to circadian preference [19]. On the whole, most of the studies in Caucasian children (e.g., [20]), adolescents (e.g., [20, 21]), and young adults (e.g., [22]) found a consistent pattern of results with a higher prevalence of evening types among those born in seasons with long photoperiods, and a higher prevalence of morning types among those born during short photoperiod seasons, in line with the results observed in mice by Ciarleglio and colleagues [17]. This pattern of results could be usefully interpreted according to the photoperiod at birth hypothesis [23], with people born during long photoperiods setting their internal clocks according to longer days compared to those born during short photoperiods. As a result, the former should show a phase delay (i.e., tendency toward eveningness) compared to the latter (i.e., tendency towards morningness). Natale and Di Milia [24] successfully tested this hypothesis by assessing the relationship between season of birth and circadian preference in Caucasian university students living in the northern (Italy) and southern (Australia) hemisphere. They found an inverse relationship between hemispheres, in the direction of a higher prevalence of morning types among those born during seasons with short photoperiods and a higher number of evening types among those born during long photoperiod seasons. While the previously reviewed studies investigated Caucasian populations, works on Asiatic children [25], young adults [26], and adults [27]

failed to point to a significant effect of season of birth on circadian preference. These discrepant findings could be explained within the framework of differences between these populations in ocular photosensitivity [28] and polymorphisms of circadian clock genes [29]. As regards the circadian clock, previous studies in mammals have clarified that its functioning is grounded on a genetic-based negative feedback loop mechanism (see [30], a review). The first description of a negative feedback loop mechanism of the Period gene in *Drosophila* by Hall, Rosbash, and Young was awarded with the Nobel Prize for Physiology or Medicine in 2017 [31]. In mammals, several circadian clock genes have been identified, such as Clock, Per1, Per2, and Per3. Although specific polymorphisms of circadian clock genes have been associated with a higher risk of diseases like multiple sclerosis [32], for example, or with the higher probability of being a morning type [33], genetic contribution is not enough to completely explain human behaviour as shown in this second paragraph about the environmental effect on the still-developing circadian timing system.

Emergence and Consolidation of Circadian Sleep/Wake Cycle

The emergence and consolidation of the circadian sleep/wake cycle in human infants represents an important developmental task that attracts the attention not only of parents, as expected, but also of psychologists, chronobiologists, and paediatricians. Although several studies have been carried out, the last word has yet to be said regarding the age of emergence and consolidation of the sleep/wake cycle in humans. While the emergence of a difference in activity between night and day, which could mirror the sleep/wake cycle, has already been observed in the first month of life [34, 35], the consolidation of this rhythm is thought to occur later, within the third month of life [16] or in the second half of the first year [34, 36, 37].

Circadian Sleep/Wake Cycle and the Two-Process Model of Sleep Regulation

The organization of the sleep/wake cycle circadian rhythm can be usefully understood within the framework of one of the still prevalent theoretical models in the area of sleep research, i.e., the two-process model of sleep regulation [38, 39]. This model posits the existence of a circadian (C) process and a sleep (S) or homeostatic process that continuously interact during the 24 h cycle to auto-regulate sleep. The C process varies according to the time of day with a sinusoidal trend, reaching the acrophase at around 17:00-18:00 h and the nadir at around 04:00 h. The S process exponentially increases its value in relation to the lengthening of wake and sleep starts when a critical value is reached, i.e., when the S process comes close to the upper threshold of the C process. During sleep, the value of the S process decreases in relation to the increase of hours of sleep reaching the level observed during previous wake. The awakening occurs when the S process reaches the lower threshold of the C process. Slow-wave activity during NREM sleep is considered the main marker of the S process while the rhythms of body temperature and melatonin, which are inversely coupled, are considered the main markers of the C process. While the anatomical substrate for the S process is yet to be clearly identified, the C process is generated at the level of the SCN by the endogenous circadian clock [40]. It is possible to suggest that a unique anatomical reference center may not be necessary for the S process because such a process is more pervasive in comparison to the C process. Indeed, while the C process can be viewed as an orchestra conductor who coordinates several musicians, potentially explaining the reason why an anatomical substrate has been disclosed, the S process triggers some retroactive feedback servomechanisms, aimed at keeping the internal environment constant, and thus reducing the need for a single reference center.

Developmental Changes According to the Two-Process Model of Sleep Regulation

Looking at the two-process model from a developmental perspective, it could be supposed that the S process may be preponderant over the C process in early life, with electroencephalographic markers of the S process appearing in the very first few months of life [41]. It is possible that the prevalence of the S process over the C process at birth could be due to the high sleep requirement in infants, which could be evolutionarily adaptive bearing in mind the potential role played by sleep at this stage of life in, for example, long-term memory consolidation [42] and cortical development [43]. Furthermore, in line with a possible earlier appearance of slow-wave sleep [44], it could be supposed, generally speaking, that from a phylogenetic point of view the S process may be preponderant over the C process in early life because homeostasis is an intrinsic basic of living beings, aimed at avoiding the possible interference of the environment. When growing up, the need for sleep decreases [45] and slow-wave activity (a marker of the S process) also decreases, particularly during puberty [43] and adolescence [43]. In line with these data, Jenny and colleagues [46] have shown that the accumulation of homeostatic sleep pressure was slower in post-pubertal adolescents compared to pre-pubertal children. This maturational change in the S process during adolescence seems to allow for the appearance of a preponderant C process. Indeed, the C process, which aims to help the S process to gradually tune with environmental changes, undergoes a progressive development that is completed at the end of adolescence [47], a period of life that is characterized by the circadian timing system's higher sensitivity to light [48]. During this precise stage of life, a phase delay in the circadian timing system [49], which has mainly been thought to be prompted by pubertal maturation, has consistently been reported, not only in humans but also in other mammals (e.g., rhesus monkey) [50, 51]. While the C process seems prevalent in adolescence over the S process, aging is associated with a weakening of the C sleep regulation process, as pointed out by Cajochen and colleagues [52], leading to less consolidated sleep. Supporting this hypothesis, some

experimental evidence has highlighted the possible neural substrate of this age-related decline in the C process of sleep regulation. In particular, Nakamura and colleagues [53] showed a degradation of neural activity rhythms at the level of the SCN with aging in mice, in line with post-mortem studies in humans [54].

Individual Differences in Circadian Rhythm

Individual differences in both circadian and homeostatic sleep regulation [55] can separately contribute to the emergence of circadian preference [19], which is commonly acknowledged as one of the most robust individual differences in circadian rhythm. Although measurement of circadian preference through biological markers (for example through the recoding of body temperature) is preferable because it is more accurate, this kind of assessment is often impracticable in large-scale studies due to the high cost. For this reason, the assessment of circadian preference is commonly carried out through questionnaires, with the Morningness-Eveningness Questionnaire (MEQ) [56] being the most widely used questionnaire throughout the world. A variant of the MEQ for children and adolescents is available; this questionnaire has been successfully validated through objective external criteria such as monitoring of body temperature and actigraphic recording of sleep/wake cycle [57]. In the MEQ the use of open questions concerning the subject's ideal bedtime and get-up time allows researchers to compute the ideal midpoint of sleep, i.e., the clock time that splits the interval between the ideal bedtime and get-up time in half. The ideal midpoint of sleep is commonly acknowledged as a reliable marker of sleep timing preference because it is more strongly correlated with the overall score of the MEQ [58]. A later ideal midpoint of sleep points to a preference towards eveningness, while an earlier ideal midpoint of sleep points out a preference for morningness. From a developmental point of view, as can be observed in Figure 9.1, morningness is more prevalent than eveningness during childhood. A

shift to higher prevalence of evening types has been consistently observed in adolescents of different nationalities, leading to the supposition that mainly biological factors (e.g., pubertal maturation) may be involved in this shift. The maximum tendency toward eveningness is reached at around 20 years of age [47, 59] and afterwards, a shift toward morningness preference begins, leading to a higher prevalence of morning types in adulthood [47, 59, 60]. The end of the shift toward eveningness combined with the beginning of the shift back toward morningness at around 20 years of age has been proposed as a biological marker of the end of adolescence [47].

Conclusions

Although the development of the circadian sleep/wake cycle is yet to be fully understood, the two-process model of sleep regulation provides a useful theoretical framework that allows us to derive some conclusions.

In early life the S process may be preponderant over the C process due to the latter being less “mature”. Indeed, the C process may be programmed to help the S process to gradually tune with the environment. The example of prematurely born infants could support the view of the gradual development of the C process, which is completed at the end of adolescence and becomes preponderant over the S process. Indeed, preterm infants’ early interaction with a *sui generis* environment that is characterized by a more regular temporal pattern (e.g., the regular pattern of feeding in neonatal care units) [5] may result in a reinforcement of the C process. This reinforcement of the C process could lead to the early consolidation of the circadian sleep/wake cycle in prematurely born infants [3].

As already pointed out, the topic of the emergence and consolidation of the sleep/wake cycle in infants attracts the attention of several figures, such as parents, psychologists, chronobiologists, and paediatricians. Parents, in particular, should be aware of

the potential positive outcome of circadian milk as a powerful form of chrononutrition [10] which seems a highly promising strategy to produce an early consolidation of the sleep/wake cycle [14]. Furthermore, parents should consider that “immersing” their babies into the environmental rhythmicity could promote a circadian development that is in harmony with the environment. Indeed, light is able to act on the circadian timing system even when infants are sleeping [61]. Moreover, parents should also be aware of the importance of the regularity of meals to favor a harmonious development of the C process with the environment. For example, it has been shown that skipping breakfast, an adjustable risk factor, is associated with a higher body mass index [62]. Indeed, skipping breakfast, apart from producing a lower satiety level that could explain a higher food intake, negatively affects the clock gene expression, leading to an increase in the postprandial glycemetic response [63]. Since the S process is preponderant in early life, concurrently with strategies aimed at facilitating the appearance of the C process, it should be opportune to protect the homeostatic mechanisms. For example, sleep deprivation in children, the effects of which could be more detrimental than those observed in adults in which the two processes work equally, should be avoided through interventions of sleep hygiene [64] aimed at protecting the S process.

Another example of possible intervention on the C process regards adolescents. As previously highlighted, a phase delay of the circadian timing system occurs in adolescence [49] that in some cases could lead, along with other factors, to the so-called delayed sleep phase disorder (DSPD) [65]. It is known that DSPD has higher prevalence among adolescents and has several negative outcomes on health and social life [65]. A potential intervention aimed at counteracting the negative effects of DSPD is represented by light therapy, which is commonly acknowledged as an effective treatment of circadian rhythm sleep disorders [66], with light acting as a key regulator of the C process.

In spite of the phase delay in the circadian timing system that commonly occurs during adolescence, school start time (a social synchronizer) does not change according to this biological phase delay. The lack of synchrony between the biological and social clock is the so-called social jetlag [67], that reaches its maximum extent during adolescence [68]. Social jetlag has been associated with several negative outcomes, such as obesity [68] and poor academic performance [69]. One potential intervention aimed at reducing social jetlag consists in acting on the C process by delaying school start time. A systematic review [70] has shown that delaying school start time by between 25 and 60 minutes can decrease daytime sleepiness and depression.

To sum up, within the theoretical framework of the two-process model of sleep regulation, two macro-categories of interventions can be suggested: on one hand, the interventions on the S process are mainly protective/collaborative, while, on the other, those on the C process are mostly educative. The interventions on the S process could be more effective if carried out in the family context; for example, the role of parents is of primary importance in order to help children to practice good sleep hygiene, thus reducing the risk of sleep deprivation. To this end, formative activities specifically addressed to parents could be devised. As regards interventions on the C process, the role of society should also be taken into account with, for example, legislative interventions aimed at delaying school start time, since this tactic has proved to be effective at reducing some consequences of social jetlag. A future research task would be to provide data concerning both types of intervention.

To conclude, this chapter has shown that, by examining the developmental changes of the sleep/wake cycle according to the two-process model of sleep regulation, some interventions can be scheduled in order to consolidate the sleep/wake rhythm in early life or to prevent/solve some issues due to the maturational changes of sleep regulation processes.

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Figure Legend

Fig. 9.1. Variation of the ideal midpoint of sleep across the human lifespan. Datapoints refer to an overall number of 11.418 persons aged between 10 and 78 years old, of whom 7.225 were females and 4.193 males. The ideal midpoint of sleep reported here derives from the administration of questionnaires aimed at measuring circadian preference in several studies carried out by the research group coordinated by Professor Vincenzo Natale at the Department of Psychology of the University of Bologna (Bologna, Italy).

Fig 9.1

