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Current Opinion in Behavioral Sciences

Effects of light exposure at night during development

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Disruption of the circadian system is increasingly prevalent in modern society. The mammalian circadian architecture is functional from birth and continues to develop throughout the early postnatal period. Importantly, light is the most salient entraining signal for the circadian system. Early life experiences can profoundly affect the developing brain, influencing adult behavior, health, and disease; thus, the immature circadian system may be particularly sensitive to circadian disruption. Indeed, early lighting environment impacts the maturation of the circadian system. The consequences of early light experience persist into adulthood influencing physiological and behavioral functions that are regulated by the circadian system. This review will discuss the development of the mammalian circadian system and implications of disruptive light exposure during early critical periods.

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Current Opinion in Behavioral Sciences 2015, **7**:xx–yy

This review comes from a themed issue on **Development and Behavior**

Edited by **Frances A Champagne** and **Anthony R Isles**

doi:10.1016/j.cobeha.2015.10.008

2352-1546/Published by Elsevier Ltd.

Introduction

Circadian rhythms are endogenous cycles of physiology and behavior that have periods of about 24 hours (h). These rhythms are aligned to the timing of the daily rotation of the planet and are most potently synchronized by light information. The presence of a functional circadian system is evolutionarily advantageous, dramatically improving the odds of survival when an individual is entrained to its environment. Although entrainment to the external day/night cycle is no longer crucial for human survival, circadian disruption produces a host of deleterious outcomes. For instance, shift-work which causes chronic circadian disruption is associated with increased risk for developing cardiovascular and reproductive disorders, certain types of cancer, gastrointestinal issues, obesity, and affective disorders [1].

Early life experiences can alter brain structure and function, profoundly influencing adult behavior, health, and disease. Although a number of excellent recent reviews have focused on how social and spatial early life environmental perturbations influence development, there has been little focus on aspects of the circadian environment during development (for example: early life circadian disruption, environmental light exposure, and sleep timing). Emerging literature suggests that the lighting environment in which an animal is reared significantly affects the development of the circadian system and has long-term implications for adult physiology and behavior [2]. This research is particularly salient, as environmental lighting has dramatically changed over the past 150 years. Modern technology, and particularly electric light, has uncoupled humans from the 24 h day to which our bodies have evolved.

The vast majority of research investigating physiological consequences of light at night and urban 'light pollution' focuses on adults and in particular shift-workers. However, social jet-lag, which is a misalignment between an individual's circadian clock and social clock, affects ~70% of the population in westernized societies [3••]. Further, over 99% of the population in urban environments is exposed to unnatural light at night. Because the development of the circadian system is incomplete in early life, exposure to unnatural lighting environments may have particularly profound effects on physiology and behavior at this time. In this review we will first provide a background on the development of the circadian system. Next, we will describe how environmental lighting affects the developing circadian system. Finally, we will summarize recent literature demonstrating the consequences of early-life circadian disruption.

Development of the circadian system

The mammalian circadian system can be divided into a physiological and a molecular component. The physiological component comprises three important elements: light is first detected by the retina and secondly transmitted by the retino-hypothalamic tract (RHT) to the suprachiasmatic nuclei (SCN) of the hypothalamus thirdly, which is considered the master circadian oscillator (Figure 1). Within the SCN, the molecular component of the clock controls circadian rhythms by an autoregulatory feedback loop of key circadian clock genes. Most tissues and cells throughout the body rhythmically express circadian clock genes; the SCN synchronizes these rhythms

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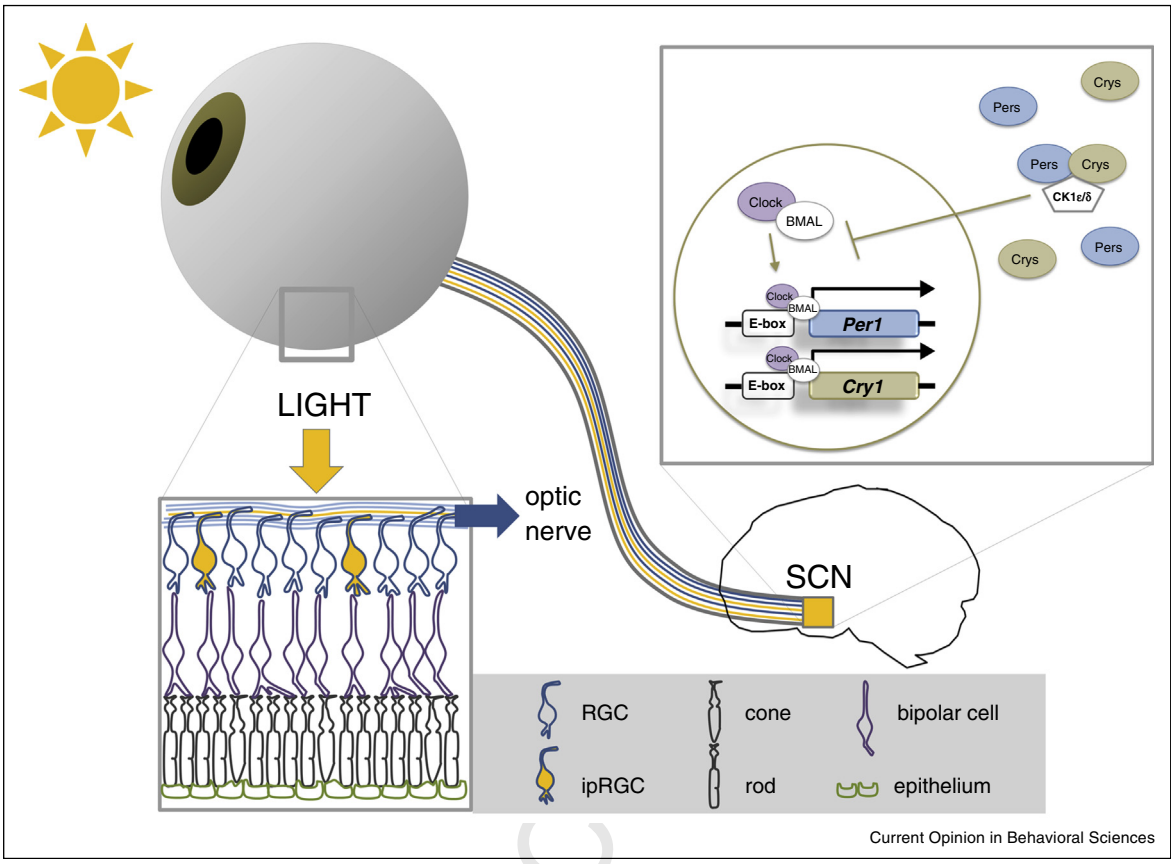
Figure 1



Physiological components and molecular mechanisms of the circadian system. Light activates intrinsically photosensitive retinal ganglion cells (ipRGCs; 1–3% of all RGCs), which project axons through the retino-hypothalamic tract (RHT) to the suprachiasmatic nuclei (SCN) of the hypothalamus. The molecular component of the clock controls circadian rhythms within the SCN by an autoregulatory feedback loop of circadian clock genes: circadian locomotor output clock kaput (CLOCK) and brain and muscle arnt-like protein 1 (BMAL1) form a complex that binds to the e-box in the promoter regions of the *period* (*per*) and *cryptochrome* (*cry*) genes to activate transcription. Per and Cry proteins accumulate in the cytoplasm and upon reaching a critical threshold form a complex along that translocates back to the nucleus and interacts with CLOCK and BMAL1 to inhibit their own transcription. Light intensity, duration, and periodicity control oscillations of these key clock genes. In turn, SCN neurons regulate peripheral clocks (in nearly every cell of the body) via neural and humoral mechanisms.

by transmitting time-of-day information via neural and endocrine pathways.

Physiological components

The retina contains three main photoreceptors: first, rods; second, cones, and third, intrinsically photosensitive retinal ganglion cells (ipRGCs) (Figure 1). Whereas rods and cones are primarily (although not exclusively) involved in image forming visual function [4], ipRGCs are the primary photoreceptor for conveying light information to the SCN and entraining circadian rhythms [5,6]. The function of ipRGCs is dependent on the photopigment melanopsin, which is detectable in mice as early as embryonic day 10 (E10). In mice, ipRGCs are light responsive from birth and form functional connections with the SCN [7]. This suggests that the murine retinohypothalamic tract is present at birth [8,9] (although this may vary between species [9]). The strength of this pathway gradually increases, until the adult pattern is achieved around postnatal day 10 (P10).

Although ipRGCs are the primary photoreceptors for conveying circadian information, rods and cones also provide circadian input. In melanopsin knockout mice, circadian rhythms remain entrained by light, demonstrating rods and cones contribute to non-image forming light information. In mice, rods and cones become photosensitive between P4 and P14 [10,11] and the ipRGC depolarizing response to light changes dramatically once functional rod and cone input is established [12•].

Understanding how and when the circadian system develops in human infants is limited, due to obvious ethical limitations. However, some information has been gleaned

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by studying pupillary reflex. In addition to projecting to the SCN, ipRGCs control the pupillary light reflex in mammals via projections to the pretectal nucleus. The pupillary light reflex emerges in preterm human infants between 30 and 35 weeks gestational age (indicating ipRGCs are functional and connected to the pretectal nucleus) [13]. Preterm infants also entrain to low-intensity cycled light. Taken together, these results suggest that there are functional connections between ipRGCs and the SCN at this time [14]. In humans, the circadian system progressively develops between one and three months of age, gradually organizing physiological (temperature and hormone secretion) and behavior (rest/activity) activity in a 24 h cycle [15]. Furthermore, circadian rhythms may emerge before one month of age; a case study in a healthy male infant showed that circadian rhythms in temperature appear within one week of birth [16].

Molecular mechanism

Rhythmic patterns in gene expression underlie circadian activity in most organisms. In mammals, circadian locomotor output clock kaput (CLOCK) and brain and muscle arnt-like protein 1 (BMAL1) form a complex that binds to the e-box in the promoter regions of the *period* (*per*) and *cryptochrome* (*cry*) genes to activate transcription. PER and CRY proteins accumulate in the cytoplasm and upon reaching a critical threshold form a complex that translocates back to the nucleus and interacts with CLOCK and BMAL1 to inhibit their own transcription (Figure 1). This cycle takes approximately 24 h and is also influenced by additional regulatory circadian proteins [(reviewed in 17)]. Because of the difficulty in studying gene expression in humans, all of the results described in this section are from rodents. Rhythmic expression of PER proteins begins as early as E18 in the SCN of mice, with the amplitude of the rhythms increasing to adult levels between P2 and P10 [18]. Other core clock proteins including BMAL1, CLOCK, and CRY1 are present in the SCN at E18, but are not rhythmically expressed until after birth. Embryonic rhythms in circadian clock proteins probably have functional consequences; for instance, rhythmic glucose consumption and SCN firing are detectable before birth [19,20].

In mammals, the SCN provides time-of-day information (via neural and humoral mechanisms) to many other central and peripheral tissues, which also display circadian oscillations [(reviewed in 17)]. During development, peripheral rhythms in circadian clock genes emerge after circadian rhythms in the SCN. Circadian rhythms in liver, thyroid, adrenals, colon, and pineal gland are evident from the time of birth, but do not develop in some tissues, such as lung, until P10. Furthermore, the phase of peripheral circadian rhythms continues to shift and does not reach adult phases/amplitudes of rhythmicity until around the time of weaning [21,22•]. The molecular machinery for generating circadian rhythms is present before intact rhythms in clock genes emerging. For example, circadian variation in clock genes is absent in mouse embryos. When embryonic tissues are placed in culture, however, PER2 bioluminescence rhythms are observed [23]. This suggests that although embryonic tissues are capable of circadian rhythms, the entraining signals may be insufficient for synchronizing peripheral rhythms in embryos.

Influence of light on circadian system development

One key feature of the circadian system is that when an animal is placed in constant conditions it will continue to display near 24 h patterns in physiological and behavioral functions. These rhythms, however, are not exactly 24 h: nocturnal rodents typically display rhythms slightly less than 24 h and rhythms in diurnal humans are typically slightly longer than 24 h. Thus, the entrainment of the circadian clock to exactly 24 h is essential to prevent a gradual misalignment with the external environment. Beginning soon after birth, environmental light is the most salient cue for entraining SCN oscillations. As mentioned, light information is transmitted from ipRGCs through the RHT to the SCN. Within the SCN, light induces activation of immediate early genes and time-of-day dependent changes in *Per* gene expression in male hamsters [24].

In rats, light pulses at P1 induce *Per1* expression in the SCN and *Per1* induction becomes gated (meaning induction is dependent on time of day) by P3 [25]. This indicates that light affects core molecular clock mechanisms within the SCN immediately after birth. The photoinduction of *Per2* develops after *Per1* around P3 and substantial postnatal maturation of the circadian clock occurs with complete gating of photoinduction of c-fos developing around P10 [25].

Although this review focuses on the effects of light on the circadian system during development, maternal signals also regulate development of neonatal and fetal circadian systems in rodents (discussed in Ref. [26]). Changes in the duration of daily light exposure alter several key maternal behaviors including nursing, contact time, and licking and grooming [27]. After SCN responses to light attain mature levels, the molecular core clockwork probably begins to entrain to photic cues and maternal entrainment gradually loses importance [26].

Early lighting environment can alter the development of the circadian system. Indeed, lighting environment during the perinatal period targets long-term adaptive responses of the circadian clock to future environmental lighting. After exposure to early life constant lighting, Per1:GFP reporter mice had uncoupled circadian rhythms in the SCN; moreover, upon re-exposure to constant light in adulthood, the mice displayed weaker

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locomotor activity rhythms [28]. However, other studies have reported conflicting results. For example, Brooks and colleagues demonstrated that exposure to constant light during development amplified PER2:LUC rhythms at the SCN level. This conferred resilience to the disruptive effects of constant light exposure during adulthood but resulted in a shorter circadian rhythm period [29•]. Further work from this group demonstrated that darkness during early life is critical for the normal development of circadian behavior [30].

Changes in the duration of daily light exposure, also known as photoperiod, can also alter circadian activity in both photoperiodic and non-photoperiodic rodents [27]. Mice exposed to long days (16:8 light/dark cycle) during the perinatal period demonstrated shorter behavioral activity when placed in constant darkness later in life. These changes in behavioral activity correlated with narrowed waveforms of *Per1* promoter activation in the SCN [31]. Further, early life photoperiods have a lasting influence on retinal and visual function, probably by modulating developmental programming of retinal dopamine [32••].

SCN rhythms are more malleable in early life and can adjust to varying light cycles. For example, exposure to non-24 h light cycles (e.g., light:dark 11 h:11 h) reprograms the SCN by plastic DNA methylation in young mice (three week old), but not adult (nine month) mice [33••]. This highlights the importance of having a stable circadian lighting environment, particularly during development.

Clinical studies in human infants show that light cycles affect biological rhythms and sleep states, indicating the biological clock also begins to respond to light at an early age in humans [34]. Cyclic light/dark cycles are generally recommended for early life lighting in humans and there is ongoing research to determine optimal indoor lighting across the lifespan [35•]. There is no clear-cut scientific consensus, however, and many neonatal intensive care units (NICUs) do not have specifically planned light cycles or employee alternative lighting strategies such as continuous dim or bright light [36•]. Progress in defining lighting recommendations for NICUs has been challenging due to limitations in studying the effects of environmental lighting on infant developmental progress (e.g., other factors such as prematurity of the infant, institution, and social situation of the family often obscure the effects of environmental lighting) [36•].

Consequences of early-life lighting environment

Early life experiences produce effects that can persist throughout life. As described above, the circadian system is functional from an early age and can be programmed by early-life environmental lighting. Thus, what are the physiological and behavioral consequences of light exposure during development?

In adult male and female rodents, exposure to unnatural light cycles elicits increases in depressive-like responses [37–39]. Exposure to aberrant light cycles during development can also deleteriously affect adult behavior. Indeed, both male and female mice exposed to dim light at night during the neonatal period increase anxiety-like behavior and fearful responses in both elevated plus maze and passive avoidance tests. These mice also reduced growth rates during early-life [40•]. Interestingly, exposure to constant light during development may also protect against the development of depressive-like behaviors due to constant light exposure in adulthood. Male rats exposed to constant light during development and subsequently re-exposed to constant light in adulthood did not develop depressive-like behaviors [41]. Whether early life lighting environment can similarly 'buffer' against exposure to a specific light cycle in adult humans is unknown.

Perinatal photoperiod has enduring physiologic and behavioral consequences in mammals for which reproduction is both regulated and unaffected by photoperiod. In seasonally breeding male and female Siberian hamsters, perinatal photoperiod influences affective behaviors [42] and immune function [43] in adulthood. The duration of light exposure during development also modulates both affective behaviors and short-term memory in reproductively non-photoperiodic adult rats [27]. Rats exposed to prolonged dark conditions (6:18 light/dark cycle) from P2 to P14 increased anxiety-like behaviors, reduced social interaction, and demonstrated impairments in object recognition in adulthood. Behavioral variations were accompanied by changes in HPA axis reactivity and hippocampal N-methyl-D-aspartate receptor mRNA. In this model, it was unclear whether behavioral changes in offspring were directly due to the altered light cycle or to differences in maternal care [27]. Indeed, adult wild-type offspring reared by *Clock* mutant mice exhibit increased anxiety-like behavior in adulthood, suggesting the importance of an intact maternal circadian system [44].

Clinical studies in preterm infants indicate lighting environment can affect biological rhythms and sleep states [34], postnatal weight gain [45], and crying [46]. The long-term consequences of neonatal lighting environment are unclear [36•]. However, studies investigating sleep and circadian rhythms during early life and adolescence implicate sleep and circadian rhythm disturbances in the etiology of mood disorders including schizophrenia. Youth that are ultra-high risk for the development of psychosis display increased wake time after sleep onset, increased movements during sleep, and decreased sleep efficiency as compared to healthy control [47]. Furthermore, both low and high

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concentrations of neonatal vitamin D are associated with an increased risk for developing schizophrenia [48]. Epidemiological work further implicates early life-lighting environment in the development of schizophrenia as people born in winter or early spring have a small but significantly increased risk for developing schizophrenia [49].

The majority of both clinical and basic research investigating lighting environment during development have specifically focused on neonates. However, exposure to light at night and the use of light-emitting electronic devices for reading, communication, and entertainment has greatly increased in recent years, particularly among adolescents. This highlights the need to focus on how environmental light can affect the adolescent circadian system. One study indicated that adolescents living in brightly illuminated urban areas have stronger evening-type orientations compared to adolescents living in darker municipalities. Further, time spent on electronic screen media correlated with eveningness (individuals who are most active or awake during the evening) and increased stimulant use in adolescents [50].

Adolescence is also associated with sleep deprivation, more so in industrialized societies, resulting from delayed bed times provoked by electronic screens and early school start times. Male and female adolescents with a greater tendency to delay circadian rhythms may be more likely to become sleep restricted and develop depressive symptoms [51]. Indeed, shorter sleep duration in adolescence is associated with an increased likeliness to engage in suicidal behavior [52]. Overall, dysregulation of circadian rhythms during ontogeny seems to be a prominent route to the development of mood disorders [53].

Finally, circadian disruption and exposure to aberrant light cycles are associated with metabolic disturbances in both humans and rodents [1,54–56]. For example, shift-workers are at increased risk for developing diabetes mellitus [56]. Circadian misalignment of physiology and behavior may lead to increased risk for diabetes, as a simulated shift-work protocol rapidly increases post-prandial glucose levels and decreases insulin sensitivity in healthy adults [54]. Circadian disruption and sleep disturbances may also be associated with metabolic disruption in adolescents. Children with poorer sleep scores have increased BMIs, trunk fat mass, waist and hip circumferences, and a higher odds of obesity compared to children with better sleep scores [57•,58]. Adolescents as compared to young children may be particularly at risk for the effects of circadian and sleep disruption on obesity as a study tracking sleep in children from nine months to three years of age did not find an association between sleep and adiposity [57•,58,59].

Conclusions and future directions

Aspects of the mammalian circadian system are functional from birth and continue to develop throughout the early postnatal period. Because the circadian system is immature at birth, early lighting environment can profoundly affect the maturation of the SCN and its outputs. Early lighting environment can uncouple SCN firing, alter rhythmic clock gene expression, and cause changes in DNA methylation. These changes can shape adult circadian rhythms and have important physiological and behavioral implications. Future work should establish the parameters for safe light exposures during development using animal models that are confirmed in epidemiological studies.

Conflict of interest statement

Nothing declared. All authors concur with the submission of this manuscript and this manuscript has not been previously published elsewhere.

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Please cite this article in press as: Fonken LK, Nelson RJ: Effects of light exposure at night during development, Curr Opin Behav Sci (2015), http://dx.doi.org/10.1016/j.cobeha.2015.10.008