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In utero circadian changes; facing light pollution

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In Loving Memory of Gloria Estrella Farfan

Regardless of the molecular and physiological mechanisms involved, maternal fetal circadian systems interactions are recognized as crucial crosstalk for fetal development, and in turn, it may be a key factor determining fitting health in adulthood.

However, in the last 100 years, life on the planet has altered the natural light-dark cycle by increasing light at night inducing disorganization of the circadian system, that is, chronodisruption, including perturbation of the melatonin circadian rhythm by decreasing its nocturnal peak. The reduction in melatonin is associated with gradual losses in antioxidant protection, immunological and anti-inflammatory effects and as stated by WHO, the lack of nocturnal peak of melatonin is a deleterious signal that may induce chronic disease and cancer.

Collectively the current review provides evidence about the role played by maternal circadian rhythms in fetal development and the impact of fetal-maternal desynchronization in the health and diseases of the offspring.

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Introduction

During gestation, the fetus follows a strict program that allows development and a successful transition to the extrauterine life, to which maternal circadian signals play a key role not only in the precise daily delivery of oxygen, nutrients, hormones and biophysical signals but also allowing fine coordination of the fetus with the external photoperiod. However, when the circadian signals from the mother to the fetus are interrupted or altered, the synchrony between the fetus and its mother disappear and detrimental effects are observed in fetal growth/development and postnatal physiology.

The evidence available suggests that maternal chronodisruption unsettles the fetal circadian system. Moreover, maternal chronodisruption in murine models (pregnant rats exposed to chronic photoperiod shift -CPS-), induces disarray of the circadian system in the adult offspring. The outcome is alterations in metabolic and cardiovascular physiology and lack of melatonin circadian rhythm [1–4,5•,6], as seen in Non-Communicable Diseases (NCD) that infringe our modern society.

Circadian clocks

Life in the earth evolved predictively to accommodate the individual's physiology and behavior to daily day/night changes induced by our planet rotation. In the mammals, the result is a marvelous mechanism in which integrated systems of biological clocks oscillate with a period close to a day (circa *dies*, 24 hours). Such clocks drive circadian rhythms at the cellular and systemic level, generating an internal temporal order in physiological functions tuned to the external environment. Conceptually, a circadian clock comprises three parts, an input signal that entrains the internal clock to clock-time, an oscillator with a period of 24 hours, and output rhythmic signals [7•,8]. In adult mammals, the circadian system is organized as a master clock, located in the suprachiasmatic nucleus (SCN) of the hypothalamus that commands peripheral circadian clocks located in brain areas other than the SCN and almost every organ of the body [7•,8]. Then SCN, connected to the retina by the retinohypothalamic tract, entrains to the Light-Dark (LD) cycle. Next, such information is conveyed to peripheral circadian clocks through innervation by the autonomic nervous system or through the effects on all organs of circadian rhythms like temperature, melatonin, and glucocorticoids (reviewed by Buijs *et al.* [7•] Serón-Ferré *et al.* [8] Serón-Ferré and Takahashi [9] Leliavski *et al.* [10]). At the cellular level, circadian function in the SCN and peripheral circadian clocks is sustained by the interconnected stimulatory and inhibitory transcriptional-translational feedback loops of the clock genes named Period1-3, Cryptochrome1-2, Bmal1, and Clock [11–13]. This circuit drives genes involved in major cellular

functions through binding to E-boxes in their promoters (clock-controlled genes) or by using other transcription factors as intermediaries like DBP and Egr1 [14]. The overall outcome is the 24-hours oscillation of about 10–30% of the transcriptome, impacting a wide range of physiological functions. Ultimately, the integrated network of signals linking the SCN and peripheral oscillators results in overt circadian rhythms in physiological processes like thermoregulation, sleep, melatonin/ACTH/corticosteroid secretion, metabolic status and feeding tuned to the daily light: dark cycle (reviewed by Buijs *et al.* [7•] Serón-Ferré *et al.* [8] Serón-Ferré and Takahashi [9] Leliavski *et al.* [10]).

The maternal circadian system

During pregnancy, maternal physiology changes to fulfill the increasing metabolic demands of the fetus, provide input for timely parturition and finally providing food and care for the newborn. As a result, the cardiorespiratory system, immune system, renal, hepatic and gastrointestinal function, and endocrine system differ from that of non-pregnant women [8,15]. The circadian system is not an exception. Compelling evidence support that a functional reorganization of the circadian system occur along gestation in several species [16–18].

In the same line, has been reported variations in daily patterns of immunoreactive of c-FOS (Fos proto-oncogene or AP-1 transcription factor subunit) expression in early pregnant rats in areas related to sleep/wake control, finding an attenuation of daily rhythms of FOS expression in areas known to support wakefulness, whereas FOS expression was maintained in areas that correlate with sleep [16]. Keeping in mind that FOS expression is an indirect marker of neuronal activity and also a clock controlled gene; upregulation of FOS mRNA in a neuron indicates early circadian responses, thus maternal SCN circadian rhythms are adapting through gestation. As well, a series of studies by Schrader and cols [16–18], assessing rhythms of cFos and Per2 protein expression, demonstrated a functional reorganization of the SCN during early pregnancy. In this context, our group reported a 3 hours advance in the acrophase of the circadian rhythms controlled by SCN, like activity, temperature and heart rate, between the first and last week of gestation in the rat compared with non-pregnant females [4]. Additionally, Martin-Fairey and cols, recently reported that pregnancy induces an earlier chronotype of activity in mice and woman, with decreases in total activity close to delivery [19••]. Altogether, the present evidence supports that maternal SCN is modified during gestation providing a plastic background for fetal development, that need further exploration.

Besides the SCN; maternal peripheral clocks also adjust to pregnancy condition, as shown by differences between pregnant and non-pregnant rats in liver expression of clock genes pregnant and non-pregnant rats [20,21]. The expecting human, rat and mice maintain a robust circadian rhythm of plasma glucocorticoids during gestation. Although an increase in plasmatic levels of maternal plasma glucocorticoids has been observed, the acrophase of the rhythm is maintained, and the hypothalamic-adrenal axis response to stress is markedly decreased [8,22,23]. A maternal circadian rhythm that merits our special attention is the maternal melatonin circadian rhythm. In a diversity of species the amplitude of maternal melatonin circadian rhythm increases at the end of gestation [8,24••,25,26]. Maternal melatonin, reaches the fetus, providing photoperiod information as well as contributing to the circadian synchronization between the mother and the fetus [27]. Besides, hormones like leptin, prolactin, progesterone and estrogens present circadian rhythms during pregnancy in several species, including the human [8]. Then, close to term, preceding parturition, there is a prominent rhythm in human and non-human primates maternal oxytocin and circadian rhythms in uterine activity [28]. Also, metabolic variables like plasma glucose, cholesterol, free fatty acids, and triglyceride concentrations show a circadian rhythm in the pregnant rat [4,20].

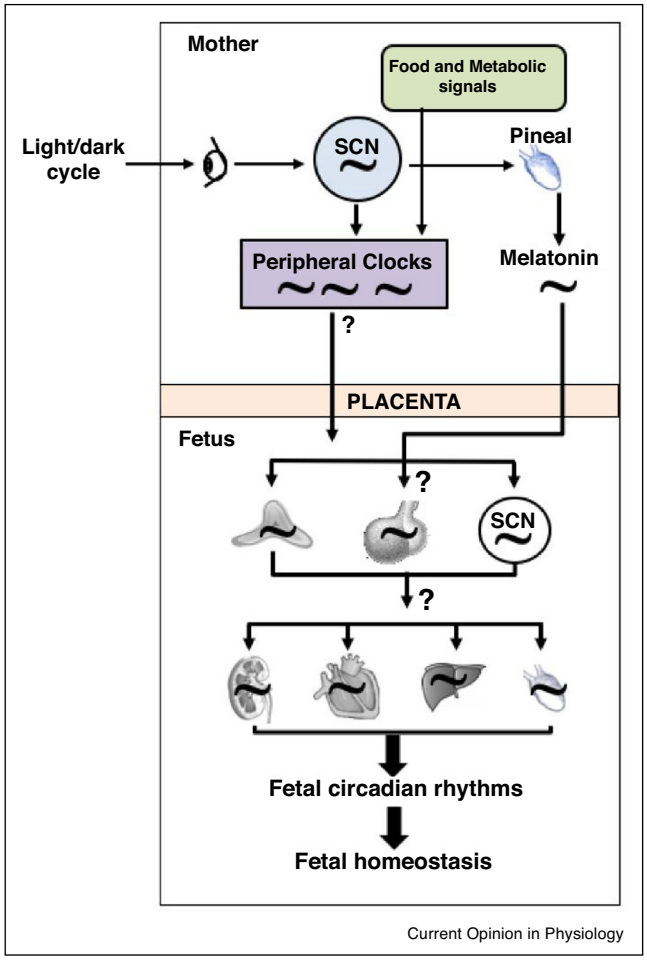
At the end, the current information supports that maternal circadian rhythm are impacted by gestation; therefore the mother will provide several redundant circadian signals to the fetus, key for fetal development. However still remains unclear how maternal circadian rhythm, with some exceptions, as described below, contribute to the fetal circadian rhythm development.

Fetal circadian system

There is ample evidence that the fetus has a circadian system, based on the expression of clock genes, in several fetal tissues in *ex vivo* and *in vivo* condition (Review in Refs. [8,26]), persistence of these oscillations *in vitro* experiments [27,29,30] and presence the circadian rhythms *in utero* such as fetal movements (human, sheep), fetal breathing (sheep), plasma hormones (prolactin sheep, adrenal steroids fetal rat, human and nom human primates) (Review in Refs. [8,26]). Importantly, these fetal rhythms are entrained to the external environment by a maternal signal. Organization of the fetal circadian system differs from the adult and the current concept is that different fetal clocks in different organs behave as peripheral oscillators entrained by the maternal circadian system. Thus, maternal signals like melatonin and food availability [12,31,32], provide a time-frame signal that contributes to the maturation of the fetus and its correct synchronization with its external media, the mother (Figure 1).

However, as an adult, the fetus would be exposed to deleterious signals when the maternal circadian system is disrupted by erroneous photoperiod, that is, maternal chronodisruption. Such situation, besides other effects

Figure 1



Schematic representation of the proposed entrainment pathways of the fetal circadian system. The fetal adrenal and fetal SCN could be entrained by the rhythms of maternal melatonin, whereas other fetal peripheral clocks are phase entrained by (1) the maternal SCN through humoral or metabolic signals that cross the placenta or (2) a fetal peripheral circadian clock. We propose that a potential candidate for this task is the fetal adrenal gland through circadian glucocorticoid production (modified from Ref. [8]).

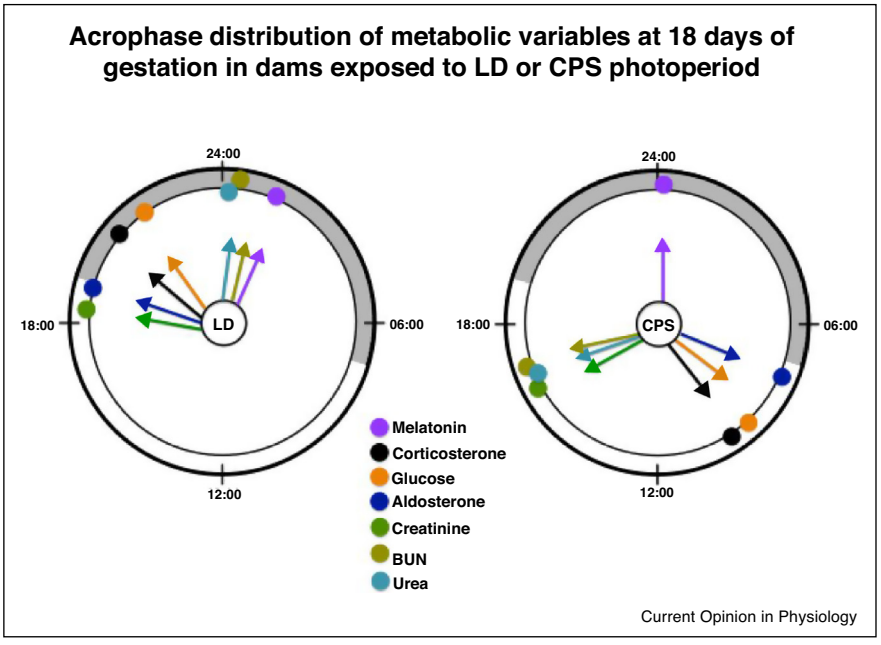
would lead to intermittent melatonin signaling, potentially inducing long-term effects in the offspring. The far-reaching effects of gestational malnutrition, hypoxia, stress on the development of adult diseases such as hypertension, metabolic syndrome, obesity, and neurologic/mental disorders have been extensively reported in the Developmental Origins of Health and Disease (DOHaD) models [33–36]. Briefly, DOHaD, as interpreted from the works by David Barker and cols, is an approach to biomedical research that highlight the impact of prenatal and perinatal exposure to deleterious environment and its role in the onset of Non-Communicable Diseases in adulthood (NCD) [37]. Given the wide-ranging unhealthy effects of our 24/7 society, maternal gestational chronodisruption maybe another player in DOHAD associated with NCD. Troublingly, cardiovascular diseases, cancers, chronic respiratory diseases, and type 2 diabetes mellitus, are responsible for 68% of global deaths, while 40% occurring prematurely (before age 70).

Long-term effects of gestational chronodisruption on the offspring

Epidemiological and experimental research studies call attention to the effect on the offspring of maternal chronodisruption induced by shift work during pregnancy. Shift work may disrupt the maternal melatonin rhythm and impose abnormal maternal sleep and feeding patterns. Epidemiological studies in women show that shift work increases the risks of spontaneous abortion, premature delivery and low birth weight babies (reviewed in Refs. [19••,38–40]). Meanwhile, in the rat, simulated shift work during pregnancy induces profound maternal metabolic changes, modified gestational length and decreases pregnancy weight gain. Importantly Chronic Phase Shift (CPS) exposure modified the acrophase of a number of circadian rhythms in pregnant rats, providing an erroneous environment to the fetus (Figure 2, From Ref. [4]). This is currently explained through phenotypic plasticity where a genotype can give rise to different physiological or morphological states depending on the prevailing environmental conditions during development. Studies in experimental animals to date show that the long-term effects of CPS in gestation would act through changes in the development of organs and tissues such as the liver, kidneys, adipose tissue, pancreas, among others.

At the present the effects on the offspring of gestational chronodisruption have been studied experimentally in several species using as models: maternal pinealectomy [41–44], maternal exposure to constant light [29,45–50] and maternal exposure to chronic phase shifts during gestation [1,4,5•,19••,51••]. These three models have in common alteration or suppression of the maternal circadian rhythm of melatonin. Keeping in mind that: a) the fetal pineal does not produce melatonin, b) maternal melatonin crosses placenta freely, originating a rhythm in the fetal circulation akin the one in the mother, c) almost all the fetal tissues studied from several species presented melatonin receptors (reviewed in Refs. [8,52••]) it is not surprising that in vivo and in vitro experiments in rat, non-human primate and sheep, demonstrated effects of melatonin on the fetal organs like adrenal, brown adipose tissue and cerebral arteries, on fetal hormonal rhythms like prolactin, corticosterone and cortisol, and fetal cardiovascular response to hypoxia and adrenal response [8,46,50,52••,53•,54,55]. Moreover, gestational chronodisruption (by alteration of the maternal melatonin circadian rhythm), is indeed, an unhealthy signal for fetal development [4,5•,6,42,47,49,56,57]. In

Figure 2

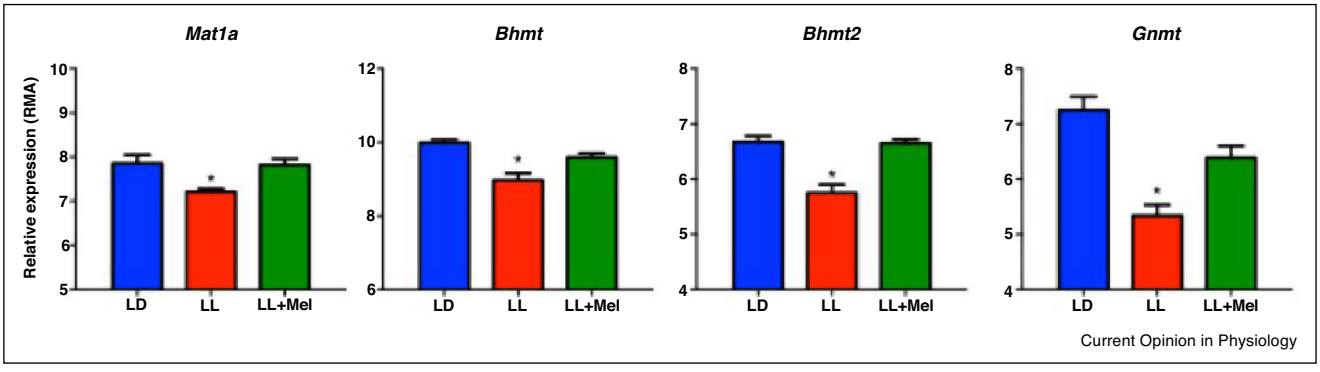


Schematic representation of acrophases distribution in maternal plasma circadian rhythms in the pregnant rats in control condition (Light dark photoperiod: LD) or exposed to chronic shift photoperiod (CPS) during gestation (for details see Ref. [4]).

keeping with the importance of the fetal environment and postnatal outcome, perturbations of the fetal circadian system by melatonin deprivation during gestation have long-term consequences in the offspring. Metabolic effects (glucose intolerance, impaired glucose-stimulated insulin secretion), and hepatic insulin resistance have been detected in the adult offspring of pinealectomized rats reared in LD [42]. In adult offspring gestated in LL, we observed a complete lack of a day/night differences in plasma melatonin and decreased day/night differences in plasma corticosterone.

Moreover, overall hippocampal day/night difference of gene expression was decreased, which was accompanied by a significant deficit of spatial memory [6]. Using a similar model we found in fetal heart that a relevant fraction of the fetal cardiac transcriptome was modified by maternal exposure to constant light, likewise in the

Figure 3



mRNA expression of enzymes of SAM ((S)-Adenosylmethionine Pathway) in fetal liver (18 DG; $n = 5$). Expression was measured by Microarray (for detail see Ref. [47]): Green: fetus exposure to light/dark photoperiod; Red: Fetus from mothers exposed to constant light since 50% of gestation and Blue: Fetus from mother exposed to constant light since 50% of gestation but receive melatonin daily in the drinking water during the subjective night (*: different to LD and LL + Mel (Two way ANOVA and Newman-Keuls as a *post-hoc*).

persistent adult downregulation of the mRNA coding for a subunit of the voltage-gated potassium Kv4 channel complex (Kcnip2) was found, that suggest enduring molecular changes which may shape the hypertrophy observed in the left ventricle of adult LL offspring [49]. Recently, we reported that the effect of maternal chronodisruption also is reflected in changes in renal function, inducing an increase in blood pressure and variability of heart rate and blood pressure [4,51••]. Therefore, chronodisruption by perturbation of the maternal pineal melatonin rhythm maybe a player in the incidence of adult diseases programmed by negative pregnancy conditions, encompassed by DOHaD concept.

Melatonin is a pleiotropic hormone involved in the fine-tuning of a vast number of physiological functions ranging from provision of temporal order, antioxidant effects, actions on cell cycle, and so on [52••]. In this context, recently has been demonstrated that melatonin has epigenetic effects by inducing differential methylation of a number of genes in cancer cells, in porcine oocytes having a protective effect over the NNAT gene involved in development [58]. In contrast, melatonin has been shown to increase acetylation of histones H3 and H4 in some areas of the rat brain and Neural stem cells [59,60]. A potential role of maternal melatonin in fetal epigenome is suggested by microarray analysis of fetal liver from fetuses gestated in constant light in which the mother received melatonin during the night (partially publish in Ref. [47]). As shown in Figure 3 the exposure to continuous light decreased the expression of mRNA encoding 4 enzymes involved in DNA methylation and importantly maternal melatonin treatment reversed the effect totally in 3 of these enzymes, and partially in the last one analyzed here, Ghmt (Figure 3). These results support that maternal melatonin modified the epigenome in the fetal liver and opens the possibility of effects in other fetal organs, impacting metabolic and cardiovascular physiology in adult life. The sort of programming that we described is conceptually similar to the programming by melatonin during gestation of the onset of puberty in seasonal mammals. In these, photoperiod, informed to the fetus by the duration of the maternal melatonin rhythm, acting on the fetal pituitary programs postnatal growth and onset of reproductive function, leading to puberty at the proper season [61].

In summary, the evidence exposed here support that gestational chronodisruption induces major changes in maternal circadian rhythms, fetal development and that these changes have an impact in the adult life at several physiological levels. Therefore, a challenge remains, in which our next step is helping to prevent the consequences of a modern 24/7 society, one that does not sleep during the night anymore.

Conflict of interest statement

Nothing declared.

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