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Reduced melatonin synthesis in pregnant night workers: Metabolic implications for offspring

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ABSTRACT

Several novel animal studies have shown that intrauterine metabolic programming can be modified in the event of reduced melatonin synthesis during pregnancy, leading to glucose intolerance and insulin resistance in the offspring. It is therefore postulated that female night workers when pregnant may expose the offspring to unwanted health threats. This may be explained by the fact that melatonin is essential for regulating energy metabolism and can influence reproductive activity. Moreover, the circadian misalignment caused by shift work affects fertility and the fetus, increasing the risk of miscarriage, premature birth and low birth weight, phenomena observed in night workers. Thus, we hypothesize that light-induced melatonin suppression as a result of night work may alter intrauterine metabolic programming in pregnant women, potentially leading to metabolic disorders in their offspring.

Introduction

Night workers experience a misalignment between their endogenous circadian timing system and behavior associated with work hours (mistimed sleep/wake; light/dark; feeding/fasting) [1–3]. In addition, light at night can acutely suppress melatonin production [4–6]. In this paper we focus on the possible risks threats to reproductive status in women undertaking night work and experiencing light-induced melatonin suppression [7]. Above all, we discuss metabolic implications for offspring due to maternal melatonin suppression.

Melatonin is an indoleamine synthesized in most animals and plants [8]. In mammals melatonin is produced primarily by the pineal gland. The light/dark cycle entrains the circadian oscillator in the hypothalamic suprachiasmatic nuclei (SCN), which in turn, entrains the pineal melatonin rhythm. Melatonin production occurs at night [9], and circulates from the pineal gland via the bloodstream and cerebrospinal fluid to other tissues of the body [10]. However, melatonin has several physiological actions besides signaling time of day or time of year information to the organism, such as its immunomodulatory [11], antioxidant [12] and cytostatic effects [13,14]. The light sensitivity of the system controls melatonin production, which together with the SCN, determines the duration of its synthesis [15]. Nevertheless, exposure to artificial light at night, as in the case of shift and night work, modifies melatonin production [16–18]. This occurs due to an acute effect of light at night on melatonin, light inhibiting its synthesis [19].

Although natural light differs to electric light, especially in terms of spectral composition and intensity, electric light is still a potent blocker of melatonin synthesis [5,6]. Moreover, recent studies have demonstrated a lower threshold for light intensity to suppress melatonin than previously reported [20]. The exposure to light at night has been shown to reduce melatonin levels with consequent circadian misalignment in night workers as discussed below [16].

Night work and health

Night work is common in contemporary society. The structure of modern society demands continuous production and/or services around the clock [21,22]. Across the world in industrialized societies it is estimated that approximately one in five workers work nights or irregular hours [23,24], where most are subjected to circadian misalignment where the behavioural cycles of sleep/wake and feeding/fasting are misaligned with the circadian timing system [25,26]. The circadian timing system is organized to facilitate behavioral and physiological adaptation (including sleep) to the 24-hour light-dark cycle [27]. In

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mammals, in addition to the "master" timing system located in the hypothalamic SCN, peripheral oscillators occur in the brain and throughout the body [28,29]. The SCN clock contributes to the regulation of body temperature, secretion of hormones melatonin and cortisol, sleep and wakefulness [30–32].

Studies investigating the effects of night work on workers' health have revealed that abnormal working hours can pose a health risk by directly acting on metabolic processes, for instance affecting body mass regulation, gut efficiency and metabolic rate [33–36]. Detrimental effects have been observed in lipid and carbohydrate metabolism, as well as in insulin resistance [37,38]. The negative impacts of night work also include changes in sleep and wakefulness [23,39], and consequent alterations in meal timing [40–42] and physical activity [43,44]. Shift work has been strongly associated with cardiovascular diseases [45], gastrointestinal [1] and metabolic disorders [46–48], and cancer [49]. Although there is less strong evidence linking shift work to mental health problems and reproduction-related problems, a few studies show its association with these factors such as depression [50], and occurrence of miscarriage [7], among other effects related to reproduction [7,51]. The social impact of changes in the pattern of family activities has also been reported [52].

Most of these adverse effects stem from misalignment of circadian timing and behavior (sleep/wake; feeding/fasting) defined by Erren et al. [25] as chronodisruption, a significant disturbance in circadian organization of the physiology, endocrinology, metabolism and behavior of living organisms, caused in part by exposure to light at night that leads to reduced melatonin synthesis [53].

Melatonin, shift work and reproductive activity

Melatonin is essential for regulating energy metabolism [54] but also for reproductive activity, promoting changes in the gonadal pituitary axis and prolactin secretion [55] and consequently modulating reproductive physiology [56,57]. Increased melatonin levels are associated with delayed puberty, and hypothalamic amenorrhea whereas decreased melatonin is found in precocious puberty [58,59]. Thus, it is increasingly relevant to study the association of melatonin with improvements in ovulation rate, luteal function and increased embryo viability [60,61]. In addition, deficiencies in melatonin production during pregnancy may alter intrauterine metabolic programming, potentially leading to glucose intolerance and insulin resistance in offspring [61–64].

Besides the acute effects on melatonin production due to light at night, shift workers may exhibit circadian misalignment and sleep deprivation which may affect fertility and the fetus, increasing the risk of miscarriage, premature birth and low birth weight [65,66]. Seron-Ferre et al. [67] analyzed the effects of circadian misalignment on the fetus and noted that this situation leads to alteration in the body temperature rhythm of newborns. Continuous exposure to light during pregnancy may increase the risk of spatial memory deficit in the adult life of the offspring in rats [68]. Most importantly, even under a light-dark cycle, the absence of melatonin in the mother during gestation impairs physical growth, neurodevelopment, and cognitive behavior in the offspring [69].

Notably, such factors (impaired physical growth, neurodevelopment, and cognitive behavior) are strong predictors of chronic diseases in adulthood. A relationship has been established between deleterious prenatal environment (e.g. malnutrition and/or fetal hypoxia) and the occurrence of diseases in adult life including hypertension, coronary heart disease, stroke, as well as metabolic and neurological disorders [70].

The mechanism by which melatonin plays a key role in the reproductive activity of numerous mammalian species [71] is via the transmission of photoperiodic information, which contributes to the seasonal modulation of reproductive activity [61]. Moreover, there is experimental evidence that maternal melatonin during pregnancy also provides a signal for the fetus [67,72]. Considering this signal follows a circadian rhythm, it suggests that a circadian pattern may be an important cue for fetal development as well to help the newborn to be entrained to the light-dark cycle after birth. Melatonin levels increases throughout the pregnancy, including in humans [73], which corroborates the idea of melatonin playing a role in fetal development.

Melatonin crosses the placenta freely and unaltered, entering fetal circulation and providing the fetus with photoperiodic signals [67,74,75]. Although circadian rhythms are established during the fetal period [76], the rhythms are initially synchronized to the mother's circadian timing system. Moreover, human fetuses have also shown circadian rhythmicity in sleep/wake and other behaviors [72,77]. The diurnal rhythmicity, however, is interrupted when mothers are exposed to constant light [78], conditions associated with melatonin suppression.

Metabolic effects due to changes in melatonin rhythm

As mentioned earlier, melatonin has an important role in optimizing energy balance and body weight regulation [79], crucial events for metabolic health [10,80]. Diseases such as type 2 diabetes, coronary artery disease, hypertension and obesity may be related to impaired intrauterine development. This phenomenon called "programming" or "hypothesis of fetal origin diseases" refers to permanent changes in the structure, physiology or metabolism of certain organs, caused by stimuli or diseases during the intrauterine development period [81,82].

Results of studies linking the external and internal environment during pregnancy to effects on body composition of the offspring, highlight that this period is crucial in the genesis of obesity and possibly numerous other diseases [83,84]. In a study with rats, Diaz and Blasquez [85] concluded that the removal of the pineal had a significant impact on plasma glucose, insulin and glucagon secretions. These authors investigated three groups of animals, controls, pinealectomized rats and pinealectomized and melatonin-treated rats. Baseline glucose, insulin and glucagon levels were evaluated after administration of arginine and glucose. The animals were kept under controlled lighting conditions, with alternating cycles of 12 h of light and dark. The results of this study indicated that the pinealectomized animals had the highest levels of glucose, the animals treated with melatonin had intermediary levels of glucose and the lowest levels were found in the controls. In addition, pinealectomized rats showed changes in insulin levels, evidenced by changes in glycogenesis and glucose uptake, highlighting to inverse relationship between insulin and glucagon levels in pinealectomized animals. Finally, treatment with melatonin partially restored the levels of insulin and glucagon in pinelectomized animals emphasizing the importance of pineal to metabolism. However, the functional interplay between melatonin and insulin was demonstrated by Lima et al. [86]. In this study, the authors showed for the first time that the absence of melatonin lead to impaired glucose tolerance and a state of insulin resistance. Later on, the same group demonstrated that melatonin, acting through its MT1 and MT2 receptors, was able to phosphorylate the insulin receptor potentiating insulin action either in the central nervous system or in the periphery [87,88].

Given melatoniṅs key role in the homeostasis of carbohydrate metabolism, Van Cauter and others [89–91] elucidated the pathways by which pineal melatonin may act as a modulator of glucose metabolism, considering that there is no pattern in glucose tolerance over the day, either through food intake or another kind of glucose intake [90]. To reinforce such an hypothesis, studies with animal models have shown increased insulin levels during the day and reduced levels of insulin concomitant with elevated glucose levels at night, concurrently with melatonin elevation [92,93]. In addition, melatonin has a stimulatory effect on glucagon and pancreatic α cells and, on the action of hepatic glucagon in the human liver [94,95]. Increased release of glucagon occurs in response to stimulation of human pancreatic cells which in turn promotes insulin secretion [96].

The action exerted by endogenous melatonin occurs through interaction with its membrane receptors, MT1 and MT2, on the cell. A reaction mediated by these receptors triggers the release of inhibitory G proteins, with consequent decrease in adenylyl-cyclase activity and reduction of cAMP. Through the use of antagonists of these receptors (4-phenyl-2-propionamidotetralin and luzindole), the importance of melatonin in the regulation of leptin expression has been shown [97,98]. Animal models have shown that the influence of feeding behavior potentially promotes physical changes, such as affecting the fat-lean mass ratio, which could lead to obesity [99–101]. Appetite hormones such as leptin may be related to this process [102–104].

The hypothesis

The cited literature suggests that aspects of modern life, such as night work and shift work, may alter circadian rhythmicity and melatonin production [105,106] in key stages of human life, such as the reproductive stage, given the fact that pregnant women may also engage in night work. Although studies on fetal programming have been carried out using animal models, there is strong evidence of reduced melatonin production in night workers as well as negative health effects. We thus hypothesize that the light-induced suppression of melatonin in pregnant night workers may affect intrauterine metabolic programming, potentially leading to metabolic disorders in the offspring.

Conclusion

In summary, there is some evidence that shift work can affect fetal development. Melatonin in some models has been shown to affect reproductive function and is important in fetal development and metabolic programming. Shift workers are exposed to light at night, which in turn is known to suppress melatonin synthesis. Based on these assumptions, we have formulated our study hypothesis.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109353.

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