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CLINICAL REVIEW

Effects of intrauterine growth restriction on sleep and the cardiovascular system: The use of melatonin as a potential therapy?

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SUMMARY

Intrauterine growth restriction (IUGR) complicates 5–10% of pregnancies and is associated with increased risk of preterm birth, mortality and neurodevelopmental delay.

The development of sleep and cardiovascular control are closely coupled and IUGR is known to alter this development. In the long-term, IUGR is associated with altered sleep and an increased risk of hypertension in adulthood.

Melatonin plays an important role in the sleep-wake cycle. Experimental animal studies have shown that melatonin therapy has neuroprotective and cardioprotective effects in the IUGR fetus. Consequently, clinical trials are currently underway to assess the short and long term effects of antenatal melatonin therapy in IUGR pregnancies. Given melatonin's role in sleep regulation, this hormone could affect the developing infants' sleep-wake cycle and cardiovascular function after birth. In this review, we will 1) examine the role of melatonin as a therapy for IUGR pregnancies and the potential implications on sleep and the cardiovascular system; 2) examine the development of sleep-wake cycle in fetal and neonatal life; 3) discuss the development of cardiovascular control during sleep; 4) discuss the effect of IUGR on sleep and the cardiovascular system and 5) discuss the future implications of melatonin therapy in IUGR pregnancies.

Introduction

Intrauterine growth restriction (IUGR) complicates 5–10% of pregnancies and is associated with increased risks of preterm birth [1], perinatal mortality, and short and long term morbidity [2]. Once born, these babies have a high risk of neurodevelopmental impairment, including cerebral palsy [3]. There is a growing body of evidence showing that IUGR can alter both the development of sleep and cardiovascular control and function in utero and this may program the fetus for life long sleep and cardiovascular related sequelae.

Melatonin is a hormone which traditionally has been studied for its function in regulating the sleep-wake cycle, however melatonin also has potent antioxidant properties. There is growing evidence from animal studies to suggest that melatonin administration during pregnancies complicated by IUGR can have both neuroprotective and cardioprotective effects [4,5]. As a result, clinical trials are currently underway to assess the efficacy of maternal administration of melatonin during human pregnancies complicated by IUGR [6]. Given the role that melatonin plays in sleep regulation, this hormone has the potential to affect the developing infants' sleep wake cycle.

Melatonin and its use in intrauterine growth restriction

Melatonin

Melatonin (5-methoxy-N-acetyltryptamine) is an endogenous neuroendocrine compound primarily produced by the pineal gland that is best known for its role in regulating circadian and seasonal timing rhythms. Circadian timing influences normal physiological processes, core body temperature, and organ function in all animals [7]. Melatonin production is controlled by the suprachiasmatic nucleus (SCN), the central circadian pacemaker, with high levels of synthesis at night, and low levels during the day. The SCN receives

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Abbreviations

AGA	appropriate birth weight for gestational age
AS	active sleep
GA	gestational age
HF	high frequency power
HRV	heart rate variability
IS	indeterminate sleep
IUGR	intrauterine growth restriction
LF	low frequency power
NREM	non-rapid eye movement
PNA	postnatal age
QS	quiet sleep
REM	rapid eye movement
SIDS	sudden infant death syndrome
SCN	suprachiasmatic nucleus

light information from the retina and sends information to the pineal gland to modulate the production of melatonin. Consequently, circulating melatonin concentration is used as a reliable marker of the phase of the circadian clock and circadian organization [8]. Melatonin also regulates sleep states, where specific inactivation of melatonin receptors (M1 or M2) can alter the percentage of time spent in non-rapid eye movement (NREM) and rapid eye movement (REM) sleep [9]. While the fundamental role of melatonin in maintenance of rhythmicity is well described, it is broadly considered a multi-faceted molecule [10]. In particular, melatonin is a very efficient antioxidant compound, but also demonstrates analgesic, anti-inflammatory and sedative properties, which may be receptor-mediated, or receptor-independent [10,11].

Due to its sleep-wake and hypnotic properties, melatonin has been used for the treatment of sleep disorders in adults and in children [12]. In this setting, melatonin as a drug is considered safe in adults and is classed as a dietary supplement in the USA. Despite its rather benign safety profile, melatonin is known to affect mammalian reproduction, with melatonin's direct actions or indirect actions via the disruption of the normal circadian rhythm, having the capacity to influence reproductive outcomes [10].

Melatonin is a potent antioxidant and free radical scavenger, induces endogenous antioxidant enzymes and has anti-inflammatory properties [13,14]. Melatonin is a direct scavenger of reactive oxygen and nitrogen species, including the highly destructive hydroxyl radical, acting in a receptor-independent manner [11]. Melatonin also acts via its receptors to stimulate production of endogenous antioxidant enzymes such as superoxide dismutase, catalase and glutathione peroxidase and reductase [15]. It is also known that melatonin receptors occur in the cardiovascular system [16] which reduce free radical formation by mitochondria [17]. Accordingly, melatonin is reported to play an important role in the regulation of several parameters of the cardiovascular system [9–11], including blood pressure, and is considered to be a putative antihypertensive agent [12–14]. It is predominantly due to these antioxidant properties that melatonin is currently being considered as a safe therapeutic to reduce brain and cardiac injury caused by oxidative stress in utero in pregnancies complicated by IUGR.

The fetus does not produce or secrete melatonin [18], and is reliant on maternal fluctuations in melatonin to entrain rhythmicity. Maternal melatonin can readily cross the placenta [19] and the fetal blood-brain-barrier [20]. After birth at term, melatonin production by the newborn does not commence for up to 9–12 wk, after which circadian melatonin cycles are observed [21]. However in preterm-born infants, rhythmic melatonin secretion is not present at 12 wk, and may be delayed for a further 3 wk [21]. This observation is important, because melatonin is believed to be important for normal neurodevelopment, and demonstrates neuroprotective benefits in pregnancy compromise [10,22,23]. Accordingly, melatonin may protect normal brain growth and development in complicated pregnancies, and when preterm birth occurs.

IUGR

Intrauterine fetal growth restriction is a concept used to describe the fetus that does not reach its genetic growth potential. This is neither a particularly useful concept clinically nor is it a diagnosis. Pragmatically, most clinicians define IUGR as an estimated fetal weight and/or birth weight at or below the 5th percentile for gestation and sex. The most common cause of IUGR is placental insufficiency but it can be associated with a number of fetal and maternal disorders such as maternal vascular disease, fetal infections, multiple births and exposure to maternal smoking during pregnancy [24]. Severe IUGR is also more common in male fetuses than female [25]. Classically, the IUGR fetus is not just small, it is also asymmetrically small, where head growth is spared relative to body growth, the so called 'head sparing' effect. This arises from fetal adaptation to reduced oxygen availability whereby the fetus enacts cardiovascular changes to redistribute cardiac output towards cerebral blood flow, at the expense of the splanchnic circulation, to optimize oxygen delivery to the brain and heart. Interestingly, in an effort to further preserve energy in a reduced oxygen environment, the compromised fetus also alters its organization of sleep states, favoring a state that requires reduced energy needs [26,27]. While these adaptations are beneficial in the short-term it may program the fetus for long-term cardiovascular [28,29] and sleep related sequelae. For example, during infancy IUGR infants are at significantly increased risk of sudden infant death syndrome (SIDS). SIDS is currently defined as "the sudden unexpected death of an infant less than 1 y of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history" [30]. It is currently believed that impaired cardiovascular control, at least in part, underpins the risk an infant failing to respond adequately to a life threatening cardiorespiratory event, such as profound hypotension [31]. In the long-term, it is well known that IUGR is associated with heightened risk of adult onset of cardiovascular disease, including coronary heart disease and hypertension [29,32,33]. Furthermore, there is evidence to suggest that IUGR alters the maturation of sleep circadian rhythms in neonatal life and sleep efficiency later in life [34]. This alteration in sleep is of concern, as sleep is the main behavioral state during the neonatal period and is known to be important for neurological development [35]. Currently, there is no therapy to treat these long-term dysfunctions. Thus, it is clear that a treatment to prevent these injuries would improve the life-long health outcomes for individuals born IUGR.

Melatonin as a neuroprotectant and cardioprotectant in IUGR

In the context of IUGR, melatonin's antioxidant properties are thought to be important because excessive oxidative stress is a likely key mechanism initiating pathways leading to both brain [23,36] and cardiac injury in IUGR fetuses [5,37]. Thus, targeting fetal oxidative stress may offer an opportunity to prevent neurological and cardiac injury in response to IUGR. There is general agreement that short-term melatonin therapy may be highly