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Chrononutrition and the role of melatonin in neonates

Chronobiologiczna rola melatoniny i jej znaczenie w żywieniu noworodków

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Abstract

Melatonin plays a pivotal role in the regulation of biological rhythms, beginning during prenatal development through maternal signalling and continuing postnatally via breast milk. In neonates, whose circadian systems are functionally immature, maternal melatonin serves as a critical entraining agent, facilitating the synchronisation of the sleep–wake cycle, supporting neurodevelopmental processes, and enhancing immune system maturation. Breast milk demonstrates distinct diurnal variations in melatonin concentration, alongside other bioactive components, establishing it as a vital chrononutritional medium. This rhythmic delivery is particularly significant for preterm infants, who lack sufficient endogenous melatonin production and are especially reliant on exogenous sources for circadian entrainment. Several factors, including the mode of delivery, maternal health, circadian alignment, and the handling or processing of expressed breast milk, may influence melatonin content and its bioavailability. Disruption of circadian rhythms, whether due to environmental factors such as continuous light exposure in neonatal intensive care units or desynchronised feeding schedules – can interfere with optimal physiological development. Recognising the chronobiological significance of melatonin opens new perspectives in neonatal care. Promoting feeding practices aligned with circadian principles, including time-of-day-sensitive milk administration, may support more favourable neurodevelopmental and immunological outcomes, particularly in vulnerable preterm populations. This knowledge has the potential to inform future evidence-based strategies in perinatal and neonatal clinical care.

Keywords: melatonin, breast milk, chrononutrition, circadian rhythm

Streszczenie

Melatonina odgrywa kluczową rolę w regulacji rytmów biologicznych. U noworodków, u których zegar biologiczny nie jest jeszcze w pełni dojrzały, melatonina pochodzenia matczynego wspomaga synchronizację rytmów okołodobowych, wpływając korzystnie na cykl snu i czuwania, rozwój ośrodkowego układu nerwowego oraz funkcjonowanie układu odpornościowego. Wykazano, że mleko matki charakteryzuje się dobową zmiennością stężenia melatoniny oraz innych związków bioaktywnych. Zjawisko to ma szczególne znaczenie w przypadku noworodków przedwcześnie urodzonych, u których endogenna produkcja melatoniny jest jeszcze niewystarczająca. Na zawartość melatoniny w mleku mogą wpływać takie czynniki, jak sposób porodu, stan zdrowia matki czy metody przetwarzania mleka. Zakłócenia w rytmie okołodobowym – spowodowane np. ciągłą ekspozycją na światło lub brakiem synchronizacji czasowej podawania mleka – mogą niekorzystnie oddziaływać na rozwój dziecka. Zrozumienie chronobiologicznej roli melatoniny oraz promowanie praktyk karmienia piersią z uwzględnieniem rytmów dobowych może przyczynić się do poprawy wyników zdrowotnych noworodków i stanowić punkt wyjścia do opracowania skutecznych strategii opieki klinicznej.

Słowa kluczowe: melatonina, mleko kobiece, chronożywienie, rytm dobowy

BIOLOGICAL RHYTHMS AND MELATONIN

Life on Earth is governed by a complex interplay of biological rhythms that regulate physiological processes, behaviour, and overall health. At the core of these rhythms lies the biological clock, an intrinsic timekeeping system that regulates various biological functions in response to environmental cues, particularly the light-dark cycle[1]. These rhythms, known as circadian rhythms, are primarily regulated by the suprachiasmatic nucleus (SCN) in the hypothalamus, which synchronises peripheral clocks throughout the body[2].

The detection of ambient light is initially mediated by the retina, which perceives variations in light intensity, duration, and photoperiodicity over the 24-hour circadian cycle. This photic input is subsequently transduced into a neurochemical signal through the synthesis and secretion of melatonin by the pineal gland. Melatonin, derived from the essential amino acid tryptophan, is primarily synthesised during the dark phase of the photoperiodic cycle. Following its synthesis, melatonin is rapidly released into the circulatory system, where it exerts systemic chronobiotic effects. The amplitude and duration of nocturnal melatonin secretion are directly modulated by the length of the dark phase, while melatonin production during the light phase remains minimal. Owing to its strict dark-dependent secretion pattern, melatonin is often referred to as the "hormone of darkness". Additionally, its seasonal fluctuations in nocturnal secretion duration allow it to function as both a circadian "clock" and an annual "calendar", playing a pivotal role in the entrainment of biological rhythms and physiological processes[3].

The regulation of melatonin synthesis follows a well-defined pathway that begins in the retina and ends in the pineal gland. Light is detected by a specialised group of retinal ganglion cells (intrinsically photosensitive retinal ganglion cells, ipRGCs), which contain the photopigment melanopsin. This enables them to sense ambient light levels independently of vision. These cells send signals to the suprachiasmatic nucleus of the hypothalamus, the body's master circadian clock. The SCN transmits circadian signals to the pineal gland via a multi-synaptic pathway that culminates in the sympathetic nerve terminals of the superior cervical ganglia (SCG). In humans, this pathway governs the release of noradrenaline, which is elevated during the dark phase and suppressed during daylight. Pinealocytes express α- and β1-adrenergic receptors, and their activation triggers an intracellular cascade, leading to an increase in cyclic adenosine monophosphate (cAMP) levels. This, in turn, upregulates the expression and enzymatic activity of arylalkylamine N-acetyltransferase (AA-NAT), a key enzyme in melatonin biosynthesis[4].

Melatonin is synthesised through a multi-step biochemical pathway, beginning with tryptophan, which is converted to serotonin and subsequently into melatonin. AA-NAT has traditionally been considered the rate-limiting enzyme in this pathway. However, studies in freely moving rats have shown that nocturnal increases in AA-NAT protein levels and enzymatic activity do not directly correlate with melatonin release, challenging its role as the primary rate-limiting factor. The final step in melatonin biosynthesis involves the methylation of N-acetylserotonin by acetylserotonin O-methyltransferase (ASMT). This enzymatic process plays a critical role in establishing the nocturnal peak in circulating melatonin levels. The circadian synthesis and secretion of melatonin by the pineal gland are key to regulating the sleep–wake cycle and overall chronobiological functions[5,6].

DEVELOPMENT OF BIOLOGICAL RHYTHMS IN NEONATES

The establishment of biological rhythms in humans begins before birth but remains immature at delivery. By approximately 30 weeks of gestation, preliminary foetal circadian rhythms begin to emerge; however, at birth, the pineal gland and SCN, though structurally present, remain functionally immature. As a result, newborns exhibit fragmented sleep–wake cycles and irregular physiological rhythms. During foetal life, the developing biological clock is influenced by maternal circadian signals, including fluctuations in melatonin and body temperature. The transfer of maternal melatonin to the foetus *in utero* plays a crucial role in regulating foetal circadian rhythms and supporting neurodevelopment. Since the foetal pineal gland is not yet capable of synthesising melatonin independently, maternal melatonin crosses the placenta and influences the developing SCN. This transfer helps entrain the foetal biological clock to the maternal light-dark cycle, thereby preparing the newborn for postnatal circadian regulation. The presence of melatonin receptors in the foetal brain as early as the second trimester suggests that maternal melatonin plays a significant role in neuroprotection, antioxidative defence, and sleep–wake cycle organisation[7,8].

The infant pineal gland is initially incapable of producing pulsatile melatonin secretion, despite the presence of noradrenaline, the neurotransmitter required for melatonin synthesis. As a result, newborns rely on maternal breast milk as an external melatonin source. Studies have shown that breast milk melatonin follows a circadian rhythm, with higher concentrations at night and undetectable levels during the day, aiding in the regulation of the infant's sleep–wake cycle[8–10].

Over the first few months of life, circadian rhythms progressively consolidate. By two to three months of age, infants begin to develop more structured sleep-wake patterns that align with external light-dark cycles, and the production of melatonin and cortisol starts to follow a rhythmic pattern, signalling the maturation of the biological clock. By four to six months, many infants establish a stable day-night sleep cycle, influenced by light exposure, feeding schedules, and parental interactions. By three to six months, most full-term infants exhibit a stable endogenous melatonin rhythm, coinciding with longer nocturnal sleep episodes. During this critical period, external zeitgebers – such as light exposure, feeding schedules, and parental care – play an essential role in entraining the infant's circadian system[8].

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Preterm infants exhibit delayed maturation of melatonin secretion compared to full-term neonates. Studies indicate that melatonin concentrations in preterm infants are significantly lower in the early postnatal period. Unlike full-term infants, preterm neonates may experience a prolonged phase of melatonin deficiency due to the immaturity of their SCN and pineal gland. Additionally, the transition from maternal melatonin supply *in utero* to autonomous production postnatally is further delayed in preterm neonates, potentially impacting their sleep–wake cycles and neurodevelopment. Consequently, breast milk, which contains higher melatonin levels at night, plays a crucial role in providing exogenous melatonin to preterm infants, supporting the development of their circadian rhythms. This suggests that interventions such as breastfeeding, nonpooled donor milk, or chrononutrition strategies could help support the circadian maturation of preterm infants. This consolidation of biological rhythms highlights the essential role of maternal chrononutritional support, particularly via breast milk, in shaping the infant's developing sleep–wake cycle and hormonal regulation[8].

BREAST MILK

During gestation, the foetus is continuously entrained to the maternal circadian, physiological, metabolic, and behavioural rhythms for approximately nine months. This intricate temporal synchronisation is abruptly interrupted at birth, necessitating an adaptive mechanism to support postnatal circadian entrainment. Maternal milk serves as a biologically optimised substitute, exhibiting circadian fluctuations in composition that align with the maternal rhythm[11].

In humans, neonates feed both day and night, with dynamic variations in the nutritive and bioactive components facilitating the infant's metabolic and developmental adaptation to the external environment. Recognising the critical role of breastfeeding, the World Health Organization (WHO) recommends exclusive breastfeeding for at least the first six months to enhance infant survival, healthy growth, and neurodevelopment. Despite this, global breastfeeding rates remain suboptimal, highlighting the need for greater public health efforts to promote and support breastfeeding practices[12].

Breast milk composition exhibits diurnal oscillations, effectively acting as a chrononutritional agent. This is particularly relevant in cases where expressed or donor milk is used, as potential temporal mismatches between milk expression and feeding times may disrupt the infant's natural circadian entrainment. Empirical studies have identified circadian rhythmicity in several human milk constituents, including melatonin and cortisol, both of which exhibit distinct peak concentrations corresponding to nighttime and morning hours, respectively. A deeper understanding of the chronobiology of lactation could inform neonatal care strategies by emphasising the optimal timing of breastfeeding and milk expression. Additionally, incorporating circadian variables into human milk research may help refine experimental methodologies by controlling for potential confounders.

Growing evidence highlights the presence of chronobiotic compounds in milk, which play a crucial role in shaping the infant's sleep–wake cycle. A recent study has demonstrated that breastfed infants establish a circadian rest–activity rhythm by six weeks of age, whereas this rhythm emerges around 12 weeks in infants receiving mixed feeding (breast milk and formula) or in exclusively formula-fed babies. Furthermore, exclusively breastfed infants exhibit superior sleep patterns compared to their formula-fed counterparts[11,13,14].

According to Oliveira et al., the rhythmic concentration of melatonin in breast milk helps regulate the infant's sleep–wake cycle, promoting longer and more restful sleep at night[10]. Several factors influence the melatonin content in breast milk, including maternal age, health, and mode of delivery. Studies have shown that melatonin concentrations are generally higher in mothers who deliver vaginally compared to those who undergo caesarean sections, possibly due to differences in stress hormone levels and circadian regulation during labour and delivery. Moreover, melatonin in breast milk is believed to contribute to gastrointestinal comfort in infants by relaxing smooth intestinal muscles, which may help alleviate colic and enhance digestion. Given its antioxidative and immunomodulatory properties, melatonin in breast milk also plays a protective role in infant health.

Qin et al. demonstrated a distinct circadian rhythm of melatonin in both preterm and term breast milk across various lactation stages, underscoring its potential clinical importance in neonatal care[15]. The highest melatonin levels were observed in colostrum, followed by transitional and mature milk, with a significant decline over the first month postpartum. Notably, preterm milk exhibited a higher peak melatonin concentration than term milk, particularly in colostrum, suggesting a mechanism supporting the underdeveloped circadian systems of premature infants. Given their heightened vulnerability, these findings reinforce the importance of breast milk – especially early lactation milk – as a natural source of neuroprotective and sleep-regulating factors in neonatal and paediatric care.

Systematic reviews by Italianer et al.[16] and Oliveira et al.[10] address crucial knowledge gaps and explore the physiological and clinical implications of chronobiological patterns in maternal milk, particularly in neonatal and paediatric care.

CHRONONUTRITION AND CONSEQUENCES OF MELATONIN RHYTHM DISRUPTION

Chrononutrition is a field that seeks to optimise nutrient intake and dietary composition in alignment with an individual's biological clock, ensuring that the timing of food consumption maximises physiological and metabolic benefits[17]. While most existing research has focused on adults, the implications of chrononutrition during early development remain insufficiently explored. Given that rest–activity cycles and nutritional requirements undergo significant changes throughout the lifespan, a better understanding of

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temporal variations in nutrient delivery during infancy is of particular clinical importance.

Neonates, unlike adults, exhibit round-the-clock feeding patterns, a phenomenon with distinct biological significance. Breast milk composition is not static; rather, it fluctuates according to maternal circadian rhythms, delivering time-dependent bioactive compounds, nutrients, and hormones that may contribute to the entrainment of the infant's developing circadian system. Furthermore, neonates exhibit sensitivity to both breast milk-derived and environmental circadian cues, which are critical for the proper maturation of their internal biological rhythms.

Beyond sleep regulation, the nocturnal transfer of melatonin via breast milk appears to contribute to reduced discomfort in infants. At two months of age, breastfed infants have been shown to experience fewer colic episodes and less severe irritability than formula-fed infants, suggesting a protective effect of milk-derived chronobiotics in promoting infant well-being[18].

Circadian rhythms play a vital role in the well-being of preterm infants. Studies have shown that premature babies in neonatal intensive care units (NICUs), who are separated from their mothers and exposed to continuous lighting experience negative health outcomes. These infants, who are unable to produce their own melatonin, exhibit lower weight gain, prolonged need for ventilatory support and phototherapy, poor motor coordination, and delayed oral feeding responses. In contrast, infants exposed to a cycled light–dark environment and fed with their mother's milk show improved weight gain, better oxygen saturation, faster melatonin rhythm development, and shorter hospital stays. Given these benefits, neonatal care societies are now recommending light–dark cycle exposure for premature infants in clinical settings[11].

Recent findings suggest a significant interplay between melatonin levels in human breast milk and maternal obesity, with potential implications for the infant's immune programming and metabolic health. In pregnancies complicated by maternal obesity, colostrum – naturally rich in immunomodulatory components – exhibits both altered immune cell function and elevated melatonin levels. This increase in melatonin may represent a compensatory mechanism aimed at restoring immune balance, as studies have shown that melatonin can enhance phagocyte function and lymphocyte proliferation, while reducing apoptosis in colostral immune cells of obese mothers[19,20]. Furthermore, melatonin's anti-inflammatory and anti-obesogenic properties have been noted to influence energy homeostasis and metabolic programming, potentially protecting the infant against the development of obesity and metabolic syndrome later in life[21]. While elevated melatonin levels in the colostrum of obese mothers may confer protective benefits, further research is needed to determine whether a threshold effect exists and how this hormonal modulation interacts with other bioactive milk components to influence childhood obesity risk.

Melatonin plays a crucial role in immune system regulation. Human lymphocytes possess melatonin receptors, allowing them to respond to fluctuations in this hormone. Studies have shown that melatonin enhances the phagocytic and bactericidal activity of colostrum-derived lymphocytes exposed to *Escherichia coli* by stimulating cellular oxidative metabolism. Additionally, tumour necrosis factor alpha (TNF-α), an inflammatory regulator found in human milk, can inhibit melatonin synthesis in the pineal gland. Caesarean deliveries increase TNF-α levels in colostrum, potentially suppressing nocturnal melatonin production, leading to inflammation and disrupting melatonin's protective effects in newborns[11,20,22,23].

Emerging evidence highlights the role of breast milk melatonin as a key modulator of the gut–brain axis during early neonatal development. Beyond its well-established role in circadian entrainment, melatonin in breast milk exhibits direct regulatory effects on the gut microbiota, influencing the maturation of the intestinal barrier and local immune responses. This interaction is particularly significant given the increasing recognition of how gut microbial composition impacts brain homeostasis and neurodevelopment via immunological and neurochemical pathways. In animal models, melatonin supplementation has been found to mitigate gut dysbiosis and neuroinflammation caused by sleep deprivation, reducing microglial overactivation and neuronal apoptosis in the central nervous system[24]. Through its antioxidant and anti-inflammatory actions, breast milk melatonin may contribute to healthy neurodevelopment by supporting a balanced gut microbiome, thereby reinforcing the bidirectional communication between the gut and brain. These findings position melatonin as a potential chrononutrient with a lasting impact on the infant's neurological and immunological trajectory.

EFFECT OF BREAST MILK PASTEURISATION ON ITS MELATONIN CONTENT

Pasteurisation, while essential for ensuring the microbiological safety of donor human milk, appears to significantly reduce the melatonin content in breast milk, potentially diminishing its chronobiological and immunological benefits. The most widely used method, Holder pasteurisation (heating at 62.5°C for 30 minutes), has been shown to cause a notable decline in melatonin levels, irrespective of whether rapid or slow cooling is employed post-treatment. One study cited in the review reported a reduction in melatonin concentrations from a mean of 51.92 pg/mL to 39.66 pg/mL after Holder pasteurisation of night-expressed milk. Given melatonin's critical roles in circadian entrainment, antioxidant defence, and immune modulation – especially in preterm infants who are highly reliant on exogenous melatonin sources – this reduction may have clinical implications. These findings underscore the need for further research into alternative pasteurisation methods or melatonin-preserving techniques to maintain the bioactivity of breast milk

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provided through milk banks[23]. In contrast, Chrustek et al. demonstrated that Holder pasteurisation preserves melatonin levels in human milk, supporting its continued use in human milk banks without diminishing this functional component[25]. As human milk banks are essential in providing safe donor breast milk to infants, particularly preterm and medically vulnerable neonates, when maternal milk is unavailable, the effects of Holder pasteurisation on melatonin content needs further investigation.

CONCLUSIONS

The findings summarised in this review highlight the critical role of melatonin as a chronobiotic hormone essential for the development and synchronisation of biological rhythms in neonates. Beginning *in utero* and continuing through early infancy, melatonin – primarily sourced from maternal circulation and breast milk – serves as a fundamental entraining signal for the immature circadian system of newborns. Its influence extends beyond sleep regulation, encompassing neurodevelopment, immune modulation, metabolic programming, and the maturation of the gut–brain axis.

Chrononutrition, particularly the temporal patterning of breast milk composition, emerges as a key physiological mechanism supporting postnatal circadian alignment. The presence of melatonin and other bioactive compounds in night-expressed milk reinforces the importance of preserving diurnal feeding rhythms, especially in preterm infants, who exhibit delayed melatonin production and rely more heavily on exogenous sources.

Despite its promising benefits, factors such as pasteurisation and maternal health status may modulate melatonin levels in milk, highlighting the need for further research into strategies that preserve its chronobiological function in clinical settings. Advancing our understanding of chrononutrition and its translational potential could lead to innovative neonatal care practices that optimise early-life health outcomes through personalised and time-sensitive nutritional support.

Conflict of interest

The author does not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

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Author contribution

Original concept of study; collection, recording and/or compilation of data; analysis and interpretation of data; writing of manuscript; critical review of manuscript; final approval of manuscript: MM.

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