Review

Postnatal Development of Pineal Synthesis and Secretion of Melatonin

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Posted Date: 30 July 2024

doi: 10.20944/preprints202407.2318.v1

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Review

Postnatal Development of Pineal Synthesis and Secretion of Melatonin

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Abstract: It is still unclear why the pineal gland is not able to start its own pulsatile synthesis and secretion of melatonin in the first months of a human's life, so that infants during this time are dependent on the external supply of melatonin via breast milk, unpooled donor milk from breast milk collection centres or industrially produced chrononutrition with melatonin-poor day milk and melatonin-rich night milk. According to current knowledge, the pineal gland and melatonin receptors are already present at birth, the suprachiasmatic nucleus is largely functional and noradrenaline, the key pineal transmitter, can be detected in the early foetal period. However, the development and differentiation of the pineal gland, the pinealocytes as the site of melatonin synthesis and the associated Lhx4 homebox only occurs during the first year of a person's life. The resulting "physiological" melatonin deficiency is associated with sleep disorders, infant colic and increased crying in babies. Intervention studies indicate that this deficiency should be compensated for – through breastfeeding, the administration of unpooled donor milk or through industrially produced chrononutrition made from unpooled cow's milk with melatonin-poor day milk and melatonin-rich night milk [1–3], see also Video [4].

Keywords: Melatonin in infants; pineal gland; noradrenaline; pinealocytes; Lhx4-Homebox; chrononutrition

Introduction

The pulsatile synthesis and secretion of melatonin in the darkness of the night is an essential unique feature of the pineal gland within circadian timing functions [5,6]. The anatomical structure of the pineal gland is already present at birth. The cells responsible for melatonin synthesis, the pinealocytes, are also present at this time.

Noradrenaline is the leading transmitter that, by activating alpha1-, alpha2- and beta1-adrenergic receptors of the pinealocyte membrane via cAMP and cGMP pathways, contributes to the activation of the pineal enzyme group including timezyme (AANAT, Arylalkylamine N-acetyltransferase) and thus to the start of pineal melatonin synthesis [7](p. 4 and Figure 5), [8](Figure 3); for detailed reviews see [8–10]. Stimulation of beta1-adrenergic receptors leads to the activation of AANAT mRNA in the cell nucleus via cAMP, inducing the pineal synthesis of melatonin [8](Figure 3). Timezyme (AANAT) is the rate-limiting enzyme in melatonin synthesis. The fibres of the nervus conarii encase the pineal gland in a tight network of fibres. At night, noradrenaline is released to the pinealocytes to stimulate the synthesis of melatonin [8](Figure 4).

Although noradrenaline and melatonin receptors are detectable in the early foetal period (noradrenaline from the 5th week in the brain stem (pons/locus coeruleus) [11], melatonin receptors in the foetal suprachiasmatic nucleus (SCN) from the 18th week [12], infants are dependent on the external supply of melatonin via breast milk in the first months of life, as they are not yet able to synthesise melatonin despite the above-mentioned structural prerequisites [1].

This is not just a "physiological" maturation process without clinically tangible consequences, because non-breastfed infants show signs of chronodisruption [13] with an increased incidence of sleep disorders, infant colic and increased crying [14,15]. The latter is associated with the dreaded Shaken Baby Syndrome (non-accidental head injury) [2].

 doi:10.20944/preprints202407.2318.v1

Stable circadian sleep-wake rhythms and increased synthesis and secretion of melatonin usually develop after the 2nd to 6th (or 17th) month of life:

- In 1982, Hartmann et al. demonstrated **reduced postnatal plasma melatonin concentrations** in 26 male infants [16]. In 1987, Attanasio et al. showed that stable day-night rhythms with high nocturnal melatonin concentrations are only detectable from the age of 6 months [17]. In 1988, Waldhauser et al. reported reduced nocturnal melatonin concentrations in the first six months of life [18]. In 2015, it was similarly pointed out that stable circadian rhythms in terms of cortisol, melatonin, sleep, temperature and the activity of circadian genes only develop in the first 6 to 18 weeks after birth [19].
- A circadian rhythm of the **excretion of sulphatoxy-melatonin in the urine** was not detectable in 26 male infants before the age of 12 weeks [16]. Kennaway et al. showed in healthy full-term infants that the excretion of this melatonin metabolite after midnight increased 5-6-fold at the age of 9-12 months compared to the age of 6 weeks (08 +/- 103 vs. 2973 +/- 438 pmol/24 h) [20]. In preterm infants, this effect occurred 2-3 weeks later [21]. Children born in February or March showed significantly higher urinary sulphatoxy melatonin concentrations at night at the age of 8 weeks compared to children born in August or September. At the age of 16 weeks, these differences had levelled out [21]. Higher secretion rates in the urine during the evening hours (6:00 p.m. to 10:00 a.m.) were associated with an earlier onset of nighttime sleep ($r = 0.51$; $p < 0.05$) [22].
- Kate McGraw et al. combined **diary method with temperature measurements** once a day for the first 6 months and, from the third week, with saliva melatonin concentration measurements once a week for 24 hours. The child was breastfed as needed. Light exposure was controlled exclusively by natural sunlight. The child's body temperature showed a circadian rhythm in the first few days of life, which stabilised after the first week. A circadian sleep-wake rhythm only developed between the 45th and 56th day of life (= 2nd month), which was associated with an increased melatonin concentration after sunset [23].
- Kleitman & Hartmann recorded a free-running non-24-hour sleep-wake rhythm in 19 infants (10 boys, 9 girls) up to the age of 4 months using **actigraphy** [24].Comprehensive current actigraphic measurements showed that 414 light- and dark-skinned infants ("1.2% female, 65.2% black") from parents of different income levels had a largely common trend, with more stable and longer nocturnal phases of motor rest developing only between the ages of 3 and 6 months [25].
- Comparable empirical data had already been recorded by William Preyer (1841-1897) in his seminal work on **developmental psychology** in 1892 [26]. His son did not start sleeping through the night until the age of 17 months [27](p. 106). In comparison to the "watered cow's milk" and "sparse wet nurse's milk" available at the time, feeding with breast milk was associated with longer sleep [27](p. 105). In the fourth month, "persistent crying without a detectable cause" was still observed [27](p. 420).

Significantly higher melatonin concentrations can be detected in breast milk at night [1,2,14,28–30], which help breastfed babies to sleep better, cry less, have less infant colic and are probably also less likely to be affected by shaking trauma.

Intervention studies involving the administration of tryptophan to infants aged 4-20 weeks have shown that they sleep better [31,32]. These trials suggest that tryptophan, as a precursor for the synthesis of serotonin and melatonin, may contribute to improving sleep in infants.

Since these studies did not analyse the relationship between age and the effectiveness of the intervention, it is not possible to assess whether the administration of tryptophan as a precursor for melatonin synthesis was also effective in the first few weeks of life. However, the following critical considerations should be taken into account:

1. The tryptophan scandal of the 1990s is a serious warning against the supplementation of industrial infant formula with tryptophan: A Japanese company had launched a tryptophan product on the market that was designed to help adults build stronger muscles. Numerous people fell ill with eosinophilia-myalgia syndrome and there were also deaths. Some data indicated that this preparation did not distinguish between L-tryptophan, the physiologically active substance, and differently configured racemates. The approval requirements were subsequently tightened internationally, so that a purity level of at least 97% L-tryptophan is

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required in tryptophan products.[33–37]. In addition, tolerable upper limits for tryptophan supplementation were proposed for adults. [38]. Subsequently, case report was published on this clinical picture following significant overdoses of L-tryptophan [36].

2. In addition, L-tryptophan can only cross the blood-brain barrier (BBB) if there is a defined concentration ratio between L-tryptophan and large neutral amino acids (LNAA) competing for BBB passage (LNAA = valine, leucine, isoleucine, histidine, lysine, methionine, threonine, tryptophan, and tyrosine)[2,39–42] and if sufficient albumin is available in the blood as a transport protein for L-tryptophan [41,43].
3. Deaths in infants and young children have been documented in chronological association with significant overdoses without medical prescription [44–46], which indicates

- that the melatonin concentrations in breast milk during the day and at night are likely to represent the gold standard for timing functions in infants, established over millions of years of evolution [2],
- that melatonin should only be administered to infants under medical supervision, for justifiable indications and in the lowest possible dosages [47–49] and
- that further basic research is needed to clarify whether, in addition to the greatly prolonged melatonin elimination half-life during infancy [1,50,51] (see discussion), other melatonin degradation pathways that have not yet been investigated [46] could be of significance in infancy.

In this context, the use of chrononutrition [2,3,32,52–61] with non-pooled day-night milk without external additions of L-tryptophan or melatonin [2,3,46] offers significant advantages. Non-pooled means that melatonin-poor day milk and melatonin-rich night milk are collected and administered separately. This applies to the administration of breast milk during breastfeeding, the administration of donor milk to premature babies via breast milk collection centres and the production of industrial infant formula from non-pooled cow's milk. The transition to such chrononutrition for infants represents a "back to nature" approach, ensuring that infants receive an adequate supply of melatonin in the first months of life [1–3].

This paper presents the current biochemical and pathophysiological knowledge on the postnatal development of pineal melatonin synthesis, the associated signal transduction chain from the retina via the suprachiasmatic nucleus (SCN) as the master clock for diurnal timing functions, via the cervical ganglion to the provision of noradrenaline in the area of the pineal gland for the activation of pineal melatonin synthesis. The usefulness of chrononutrition with non-pooled milk is derived and justified from these basic pathophysiological facts and the above-mentioned intervention effects.

Method

After extensive research on the keywords melatonin, infants, newborn, child, pineal gland, noradrenaline, timezyme, chrononutrition (in particular PubMed and patent databases) and evaluation of the bibliographies of the articles found, it was examined whether the chronobiological hypotheses mentioned above can be substantiated from a pathophysiological point of view. The present study focuses on the reasons for the physiological melatonin deficiency in the first months of life in infants in connection with the postnatal development of the pineal gland. On this pathophysiological basis, the clinical need for chrononutrition for infants is derived and justified.

Results

From an epistemological point of view, it seems important to recall the paths and pitfalls that have led to current ideas and results, or blocked them for several centuries, before presenting current molecular genetic and developmental biological data:

- Galen (129-236 BC) reported that the Greek anatomist Herophilus of Alexandria (325-280 BC) was the first to report on the pineal gland [62]. The first written evidence of the pineal gland comes from Galen himself.
- Andreas Vesalius (1514-1564) was the first to present a graphic representation of the pineal gland ("De humani corporis fabrica", "On the Fabric of the Human Body", 1543) [62].

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- René Descartes (1596-1650) considered the pineal gland to be the seat of the soul or the central point of contact between body and mind. Elisabeth of the Pfalz (1618-1680) and Christina of Sweden (1626-1689) were not satisfied with this mechanistic dualism, so they repeatedly asked where emotions could be located ("Therefore, I ask you for a more precise definition of the soul than the one in your metaphysics, that is, of the substance of the soul, which is separate from its activity, thinking." "... that I ask you to tell me how the soul of man can cause the spirits of the body to perform voluntary actions (for it is nothing but a thinking substance)." Elisabeth of the Pfalz, Letter No. 1 to René Descartes, 6 May 1643 [63]). These probing questions inspired Descartes to write his late work "De Homine" (1664), in which he wrote in 1837 in "La Dioptrique" that the pineal gland is the seat of the soul: "Let us imagine here that the main seat of the soul is located in the small gland in the centre of the brain, from where it spreads through the entire rest of the body by means of animal spirits, nerves and even blood" [62].
- Although there was already well-founded criticism of this idea shortly after Descartes' death, these speculations about the location of the soul continue to have an effect today and contributed to the fact that further functions of the pineal gland were not investigated in more detail [64].
- In 1898, Otto Heubner reported on a 4.5-year-old boy with precocious puberty and tall stature, in whom a pineal tumour was detected at autopsy [65]. This case report drew attention to the endocrinological functions of the pineal gland. The discovery of melatonin by Lerner in 1958/1959 [66,67] marked the beginning of an exponential increase in knowledge about melatonin, which continues to this day.
- In 1924, Ladislaus von Meduna (1896-1964) submitted a fundamental histological study on "The development of the pineal gland in infancy", in which anatomical preparations of 30 pineal glands from children from the neonatal period to the age of 4 (N=26) and after the age of 4 (N=4) were examined [68]. These studies clearly show that the microstructure of the pineal gland develops and differentiates in several phases only within the first year of life, so that its functional capacity is not established until several months after birth:

The vascularisation of the pineal gland would already occur from the third month of the foetal period [68](p. 535). After birth, the pineal gland would consist of "neutral ectodermal cells" until the 2nd to 4th month of life, and their differentiation into plasmatic and fibrous glial cells or into pineal cells (pinealocytes) would not occur until between the 3rd and 8th month [68](p. 546).From today's perspective, von Meduna described 100 years ago that myelinisation processes, which are a prerequisite for the transmission of information via nerve fibres in the pineal gland, only start between the 3rd and 8th month after birth:

"Typical astrocytes [as a subgroup of glial cells] in a spider-like shape with many fine processes... often condense around the nucleus in a membrane-like manner" [68](p. 542). In the 7th to 8th month of life, "the pineal gland would show the most vivid picture" because the pineal cells now develop numerous processes "to reach the nearest vessel or septum" [68](p. 544).

In a third developmental step of the pineal cells, there are bulb- or pear-shaped extensions of fibres of the pineal cells ("end bulbs"), which connect with a "dense network of strong neuroglial fibres" [68](p. 547).

Meduna suspects that the pineal gland is an endocrine organ [68](p. 547). The postnatal differentiation processes of the cells of the pineal gland described by Meduna were confirmed in 1987 by Min et al. using immunohistochemical methods on 16 pineal glands from infants and toddlers aged 38 weeks of gestation or older up to 3 years of age: In the neonatal period, predominantly pigmented type I cells were detectable, in which no neuron-specific enolase was detectable. By the end of the first year of life, type II cells with positive neuron-specific enolase then dominated [69]. These data indicate that the innervation of the pineal gland develops only postnatally, since neuron-specific enolase is considered a marker of neural maturation [70]. The importance of microglia in the postnatal networking of pineal structures (cells, nerves, blood vessels) has been extensively documented, at least in Wistar rats [71].

The mass of the pineal gland of 36 Merino sheep increased with postnatal age when compared between the 1st-6th and 9th-24th months after birth (54 vs. 66 mg during the day and 63 vs. 77 mg at night). At the same time, higher melatonin concentrations were measured at night in the 9th-24th month [72](Tab. 1-2). A similar increase in size and cellular differentiation was also observed in goats

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up to the age of 4 months [73]. In Wistar rats, cAMP signals triggered by noradrenaline to activate pineal melatonin synthesis also only become maximally effective 15 days after birth (Figure 1)[74]. In humans, this would correspond to a postnatal age of about 4.3 months [75].

Figure 1. Analysis of relative optical density (O.D.) of inducible cAMP early repressor (ICER) hybridization signal in rat pineal gland (solid line) and superimposed pineal melatonin values (dashed line). ICER nighttime values start to be significantly different from daytime values from P8 onward (P8: $P < 0.05$; P10, P15, P20, adult (Ad): $P < 0.01$). Nighttime melatonin values start to be significantly different from daytime values at P8 (P8: $P < 0.05$; P15: $P < 0.01$) [74]. With kind permission.

It has since been confirmed that the pineal gland consists of 90-95% pinealocytes, in which pulsatile pineal melatonin synthesis takes place [76,77]. More than 5000 cells of the pineal gland have been examined using single cell analysis. As a result, the following six cell types were found (pinealocytes, astrocytes, microglia, vascular, epithelial and leptomeningeal cells) [61], to which a whole series of marker genes are assigned [78], see also [77](Figure 2).

In 2023, Gregory et al. reminded us of the innervation of the pineal gland by the nervus conarii [79,80], which, as a non-myelinated postganglionic sympathetic nerve, is an essential part of the signal transduction chain between retina, SCN, superior cervical ganglion (SCG) and glandula pinealis (Figure 2).

Hertz et al. investigated the influence of these nerve fibres on Lhx4 expression in rats after SCG ganglionectomy using radiochemical in situ hybridisation [81](p. 6 and Figure 5A). The interruption of the nervus conarii eliminated the pineal Lhx4 expression that occurs in darkness. This could be stimulated again pharmacologically using isoprenaline. These data suggest that Lhx4 and noradrenaline are involved in the activation of melatonin synthesis and thus also in the activation of timezyme via the coronary nerve [81]. However, there are also unanswered questions, as extensive gene analyses have provided evidence for two pathways (phototransduction pathway and aldosterone synthesis and secretion pathway) that do not focus solely on Lhx4. However, Lhx4 can be assigned to the phototransduction pathway [81](p. 7). Figure 3 shows that the size of the pineal gland only increases significantly after birth. At the same time, Lhx4 is increasingly detectable (Figure 3).

Lhx4 is a protein that is encoded in humans by the LHX4 gene with six exons on chromosome 1q24.1-1q24.3 [82] and which, based on the above-mentioned results, is significantly involved in the control of the differentiation and development of the pineal gland. The LIM homeobox 4 (Lhx4) genes contribute to the regulation of melatonin synthesis in pinealocytes [83]. LIM genes were first detected in developing tissue types of the pituitary gland, retina, thymus, limbs, pancreatic islet cells, spinal cord and brain [84]. LIM is an acronym that refers to the associated homeodomain proteins described first (Lin-11, Isl-1, Mec-3) [84]. LIM proteins are important for organic and neuronal development processes [85]. In terms of classification, LIM domains are part of the more than 6500 known zinc finger domains. Zinc-containing polypeptides support the structural and functional flexibility of the 20 canonic amino acids found in humans [86].

Figure 2. Representation of the signal transduction chain for the activation of pulsatile pineal synthesis and secretion, with indication of the localisation of M1 and M2 melatonin receptors in the brain that are associated with sleep [87,88]. Light is converted into chemical impulses in the photosensitive ganglion cells of the retina, which stimulate the retinal formation of melanopsin. Melanopsin inhibits the synthesis of melatonin [89]. The central master clock SCN is activated via the retinohypothalamic tract. Via several sympathetic ganglia (paraventricular nucleus (PVN), upper thoracic medulla, cervical ganglion), melatonin synthesis in the pineal gland is inhibited by light or activated by darkness in the evening. The pineal gland secretes melatonin directly into the cerebrospinal fluid and via venous effluents into the jugular vein. Melatonin exerts its effects in particular via two receptor types (M1, M2), which stimulate the switch from wakefulness to sleep in the frontal pre-cortex (M1), after melatonin has induced the transition from wakefulness to NREM sleep via feedback mechanisms to the SCN (M1, M2). The thalamus, as the 'gateway to consciousness',

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is sent into NREM sleep via M2 receptors and is opened in this state – for the transfer of verbal information from short-term memory to long-term memory in the hippocampus: the consolidation of memory content takes place to a large extent during undisturbed sleep. The transition from NREM to REM sleep is induced by M2 receptors in the ventrolateral periaqueductal grey matter. During REM sleep, REM muscle atonia is generated via several neural switching points, and motor information can now be stored ('You learn to ride a bike in your sleep'). The basal forebrain is involved in these processes (M2). A highly simplified overview based on [87,90–92]. Slightly modified according to Paditz [93], with kind permission.

Figure 3. Expression of Lhx4 in the developing rat pineal gland. The arrow points to the pineal gland. Scale bar, 1 mm; E, embryonic day; P, postnatal day. ZT, Zeitgeber Time. Radiochemical in situ hybridisation for detection of Lhx4 mRNA in coronal sections of the brain from rats sacrificed at ZT6 (left) and ZT18 (middle) at the indicated developmental stages (one per row) ranging from E15 to P30. ZT18 sections were counterstained in cresyl violet for comparison (right). From: Hertz [81], with kind permission.

Discussion

The initial hypothesis that infants do not have their own pulsatile pineal synthesis and secretion in the first days and months of life is not called into question by the studies listed in Table 1. Rather, it can be assumed that the low nocturnal melatonin concentrations in newborns listed in Table 1 originate from prenatal maternal and placental sources [61,94,95]. In pregnant women, for example, melatonin concentrations in saliva of 23-25 pmol/L (= 5.35-5.81 pg/mL) were measured at 3:00 a.m., regardless of the duration of pregnancy [96](Figure 1). Immediately after birth, mean melatonin concentrations of 3 6.8, 23.8 and 32.7 pg/mL, respectively [30], see also [2](Table 1 and Figure 8) and [1](Figure 2). Qin et al. found comparable melatonin concentrations of 23.5 pg/mL in breast milk at 3:00 a.m. during the first 30 days [29].

In adults aged 25.9 ± 4.7 (20-32) years, maximum nocturnal melatonin concentrations of 101.1 ± 3.5 (18-163) pg/mL were reported. At the age of 59 ± 10.0 (49-73) years, these concentrations were lower at 49.4 ± 38.1 (14-150) pg/mL [97].

It should also be noted that the half-life of elimination is significantly longer in premature babies than in young adults (6.20 to 21.02 hours vs. 53.7±7.0 minutes) [50,98], see also [1](Table 2).

Table 1. Melatonin concentrations in the serum of newborns.

Autor (Year)	Setting	Results	Assessment
Bülbul A (2024)[99]	N=35, birth weight 3321 ± 474g, gestational age 38,1± 1 weeks, Spontaneus birth 37,2% (13/35), Caesarean section 62,8% (22/35), Female 60% (21/35), Babies stayed with their mothers, room light 6-10 lux	Serum melatonin at 2:00 a.m. (pg/mL) 19,9 ± 4,38 (9,9-26,3)	No information on the age of the babies. It can be assumed that they received breast milk (for comparative data, see above in the text).
Muñoz-Hoyos A(2007)[100]	N=35, birth weight 1800 (870-4400g), gestational age 32,5 (26-40) weeks, with respiratory distress syndrome, without sepsis. Licht: 300-450 lux in the morning	Serum melatonin at 9:00 a.m. in the group >1500g on the 1st and 7th day 104.2 ± 22.9 and 109.4 ± 24.0 pg /mL; in the group <1500g on the 1st and 7th day 63.2 ± 6.2 and 79.3 ± 6.8 pg/mL (p = 0.017)	No information on diet, so it can be assumed that the babies received breast milk. - Significantly lower melatonin concentrations in the group with a weight < 1500g.

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Sánchez-Borja C (2024)[101]	N=61 preterm infants < 25. Woche, birth weight 1350 (800-2055g), gestational age 29,9 (24-34) weeks; 65,6% (40/61) with parenteral nutrition	Serum melatonin on the 3rd day of life between 8:00 and 9:00 a.m. 30.6 (12.3 – 76.6) pg/mL	No information on oral feeding.

Based on the above-mentioned histologically detectable developmental and differentiation steps described by Meduna [68], it can be assumed that the cause of the delayed development of the ability of the pineal gland to synthesise melatonin in the first months of life lies in the development of the pineal gland itself, which only begins postnatally. Since animal data cannot be extrapolated to humans without further investigation, further studies are needed to clarify how postnatal differentiation and connection of the pinealocytes with the associated structures of the signal transduction chain from the retina to the pineal gland occurs in humans. Lhx4, noradrenaline and timezyme are likely to continue to play a leading role in this.

From an evolutionary and epistemological perspective, it is interesting that the main human rhythm generators, such as the respiratory centre with the pre-Bötzinger complex [102–105], SCN [106] and the pineal gland [81], are controlled and developed by extremely different groups of genes and pathways. According to current knowledge, however, the pineal gland does not have its own rhythm generator, but is dependent on stimulation via the SCN and noradrenaline [81].

From a chronobiological perspective, there are three possible solutions for providing infants with sufficient melatonin without external additives even in the first 3-6 months:

1. Promotion of breastfeeding. In this case, it should be ensured that the mother's milk contains hardly any melatonin during the day and that the "night milk" contains high melatonin concentrations. If milk is pumped and collected, care should be taken to collect the mother's milk in different containers, distinguishing between day milk and night milk [2]. This challenge has been pointed out by several groups of authors [1,2,14,53,55,58]. Current studies, such as Häusler et al. [61], are addressing this topic.

2. Non-pooling of breast milk in breast milk collection centres. This simple principle should also be taken into account in breast milk collection centres [2]. Studies are also being prepared for this purpose (Erler & Paditz et al.).

3. Production of formula milk. The same circadian rhythm can be detected in cow's milk as in human milk [107]. It is therefore suggested that non-pooled cow's milk be used to produce night milk, which is rich in melatonin, and day milk, which is low in melatonin. The entire production chain, from the lighting of the stalls during the day and at night, to the times when day milk or night milk should be milked and collected, and to the consideration of pH values and temperatures in the production of milk powder and infant formula infant formula has been registered in a group of patents [1–3], so that chrononutrition in accordance with scientific and regulatory standards with optimal melatonin supply for infants without artificial melatonin supplementation is possible. Es bleibt abzuwarten, ob sich spezifische AANAT-Genotypen bei Milchkühen durchsetzen, die mit erhöhten Melatoninkonzentrationen assoziiert sind [108].

Conflicts of Interest: The author declares that there are no conflicts of interest. He is a voting member of the Ethics Commission of the Technical University of Dresden, managing partner of Kleanthes Verlag für Medizin und Prävention GmbH & Co. KG, Dresden, and author of the patent application cited in this article[3].

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