

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

186,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Melatonin in Childhood Epilepsy and in Child Neurology

Justyna Paprocka, Marek Kijonka and Maria Sokół

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.80005>

Abstract

Melatonin (MLT) was isolated as a hormone by Lerner in 1958, and since then, intense studies have been under way with respect to its action and possibilities of application in various fields of medicine. Despite the existence of multiple antiepileptic medications and progress that has taken place in neurosurgical treatment of epilepsy, drug-resistant epilepsy continues to be a phenomenon that occurs in 30–35% children treated for epileptic seizures. Reports presented in the study have shown that children with epilepsy suffer from sleep disorders. Sleep deprivation may cause seizures, and on the other hand, an increased frequency of seizures may lead to sleep disturbances.

Keywords: melatonin, children, epilepsy, autism, hypoxic-ischemic brain injury

1. Melatonin

The sleep/wake cycle, body temperature, and melatonin (MLT) rhythms have a stable internal phase relationship with maximum sleepiness coinciding with the melatonin excretion peak and the core body temperature nadir in humans and other diurnal species [1]. Several genes known as *clock genes* play a role of regulators of circadian rhythms generated by suprachiasmatic nucleus among them are *PER*, *NPAS2*, *BMAL1*, and *CLOCK* [2]. Also, *Period genes* (*Per1*, *Per2*, *Per3*) and *Cryptochrome gene* (*Cry 1*, *Cry 2*) are involved in auto-regulatory translation-transcription feedback loops [3].

Melatonin, as a hormone, is secreted by the pineal gland, and its production is regulated by light and retino-hypothalamic tract. Melatonin secretion depends on the age—the highest values of its concentration are detected between 1 and 7 years of age. In healthy subjects, the

serum melatonin concentration peak occurs between 2 am and 4 am, and then it gradually declines; however, melatonin release may be shifted with time zone due to its day and night light dependence [3–5]. During the day, melatonin is not produced in measurable quantities.

Measurement of the whole 24-h rhythm of melatonin is considered to be the most robust sleep phase marker of various circadian rhythm sleep disorders [1–6]. Because melatonin secretion is suppressed by light, the melatonin levels should be measured in dim light conditions. Serial sampling of melatonin measured in the blood or saliva can be used to assess circadian timing by determining the dim light melatonin onset (DLMO), the parameter indicating the time point in which melatonin levels begin to rise in the evening above baseline [2]. Another useful circadian phase marker is dim light melatonin offset (DLMOff), the point in time when melatonin levels diminish in the morning. The melatonin secretion profile can also be analyzed in a more complex way—by approximation of the empirical or analytical models. The models of melatonin secretion can provide a set of parameters with biophysical and clinical significance that directly characterize melatonin cycle. Moreover, mathematical modeling facilitates statistical analysis of the patients' hormone levels, offering a set of parameters that enable the objectification of the secretion description.

Melatonin for many years remained the most mysterious and forgotten human hormone with not exactly understood role and suggested pleiotropic actions. It is well known that melatonin is released in a circadian pattern with a night peak. Endogenous melatonin production varies among individuals. Endogenous melatonin production varies among individuals. Melatonin is secreted mainly by pinealocytes from tryptophan through hydroxytryptophan and serotonin. Then, two enzymes, arylalkylamine-N-acetyltransferase (AA-NAT) and acetylserotonin-O-methyltransferase (ASMT), form melatonin from serotonin [1–6]. The organization of the sleep-wake rhythm is set around 6 months of age, but melatonin rhythm may be set earlier, from 3 months of age. At the age of 3, a stabilization of these rhythms is visible. Between 4 and 7 years, nocturnal melatonin secretion reaches the highest values [1–6].

Gender difference (a lower melatonin secretion in girls) and age-related decline have been described [7]. According to the latest Task Force of American Academy of Sleep Medicine, melatonin application is recommended in children with delayed sleep-wake phase disorders, children with neurological disorders, and with an irregular sleep cycle [5, 6].

Melatonin should be administered at a time related to DLMO—the onset of melatonin endogenous production [7–9]. Actually, prior to melatonin administration, DLMO should be measured to let for optimal treatment. In saliva, DLMO is defined as a melatonin range of 3–5 pg/ml [9, 10].

2. Sleep and epilepsy

A complex interaction between sleep and epilepsy is still a matter of debate. Sleep deprivation may activate epileptiform activity. Epilepsy *per se* and antiepileptic treatment may cause sleep deprivation or fragmentation causing the vicious circle.

Accumulating evidences suggest that melatonin modulates the electrical activity of neurons. Based on experimental studies, melatonin probably may mediate the GABA-ergic, 5HT-ergic,

and NO/L-arginine pathways and glutamate neurotransmission [11]. On the contrary, Steward and Leung suggested that proconvulsive action of melatonin is connected with the suppression of the GABA A receptors in pyramidal cells [12, 13]. Antioxidant properties of melatonin may also have a positive effect on children with epilepsy [14]. Our knowledge about possible melatonin role in epilepsy has increased in recent years but still remains controversial. For some time, melatonin has been recommended for children with epilepsy due to its ability to promote sleep and to avoid sleep deprivation.

Sleep problems in children with developmental disabilities and epilepsy can be connected with an improper deranged circadian melatonin secretion, an insufficient melatonin production, or melatonin receptor insensitivity. Usually, falling asleep and maintain a sleep are the most frequently encountered problems of pediatric populations. The prevalence rates of sleep problems in childhood are estimated between 30 and 40% [15–20].

At the cellular level, sleep deprivation impairs synaptic plasticity, increases hippocampal oxidative stress, and facilitates neuronal loss, which can affect neurocognitive skills especially attention, behavioral, and emotional aspects of development.

In adults with epilepsy, 55% have insomnia, 34% have sleep-onset insomnia, and 52% have maintenance insomnia [15–20]. On nights with seizures, patients experience up to 50% reduction of REM sleep and an increased REM latency [15–20]. In specific childhood epilepsy syndromes, like juvenile myoclonic epilepsy, the sufficient amount of sleep may completely protect from seizures. In autosomal-dominant nocturnal frontal lobe epilepsy, the epileptic seizures dominate at night, while in juvenile myoclonic epilepsy after awakening in the morning.

The stage of sleep also matters. Seizures are rare in REM sleep, and indeed the rate of REM seizures' onset is low (0–5%) [21]. According to the studies conducted by Minecam et al. and Herman et al., most related to sleep seizures appear in stage 2 NREM sleep (61–68%), and lower rates are evident in stages 3 and 4 as 9–14% [19, 21, 22]. Some authors believe that the area of REM discharges could be an indicator of epileptic zone [17–22]. Jan et al. postulated that the occurrence of seizures may show a 24-rhythmicity and circadian occurrence pattern (**Table 1**) [23].

Sleep deprivation is one of the most frequent precipitating factors of seizures and interictal epileptiform discharges (IED). On the other hand, site epileptic seizures, epileptiform activity, or antiepileptic drugs (AEDs) may disrupt sleep pattern. The analysis of the questionnaires filled by the patients revealed that the most common sleep-related complaints are excessive daytime sleepiness (EDS), insomnia, and poor sleep quality. The other important remark is that more sleep abnormalities are concerned with focal than generalized epilepsies. Also, sudden unexpected death in epilepsy (SUDEP) is most frequent to appear between 6 am and noon [17–21]. Long-standing epilepsy can affect insula, anterior cingulate gyrus, ventromedial frontal cortex, and through their influence on cardiac rhythm may provoke SUDEP [16–22].

Antiepileptic drugs (AEDs) may affect sleep parameters. For example, a frequently administered valproic acid, due to its interaction with GABA transmission at suprachiasmatic nucleus, may lower melatonin secretion [27]. However, Braam et al. [28, 29] compared the endogenous melatonin levels in children administered with valproate and those who did not use it, and

Seizures' occurrence pattern	Sleep	Wakefulness
Seizures' types	Tonic seizures, generalized tonic-clonic seizures, frontal lobe seizures	Clonic, absence, atonic, myoclonic seizures
Relation with sleep	78% of frontal lobe seizures 20% of temporal lobe seizures	
Epilepsy with generalized seizures	Generalized epilepsy • West syndrome: hypsarrhythmia most evident in early NREM sleep • Lennox-Gastaut syndrome: paroxysmal fast activity during sleep	Generalized epilepsy of unknown etiology: JME, GTCE (on EEG spike—waves discharges most prominent in stage 2 sleep)
Epilepsy with focal seizures	BECTS (interictal epileptiform discharges activated by light NREM) • Time peak of occurrence 6–9 am for frontal lobe seizures, NFLE: 23.00–5.00 (6–12 h after DLMO) EEG-stages 3 and 4 as effective facilitator of epileptiform discharges	• Time peak of occurrence 3–6 pm for temporal lobe seizures, TLE: 11.00–17.00 (6 h before DLMO)

Table 1. Seizures' circadian occurrence pattern [23–26].

Takaesu et al. [30] observed a minimal impact of sodium valproate on the low serum levels that do not have such supposition. Carbamazepine may increase slow-wave sleep, reduce REM, and reduce awakenings and arousals [31]. Similarly, lamotrigine and valproic acid appear to stabilize sleep (more REM and slow-wave sleep) [27–31]. Newer AEDs have little effect on sleep architecture (levetiracetam) or little is known about these effects (lacosamide, eliscarbazepine, and retigabine) [31]. The direct effect of AEDs on sleep is difficult to measure because of many confounding factors, with the leading one—polypharmacy. Antiepileptic treatment with more than one drug increases the risk of obstructive sleep apnea (OSA). The prevalence of OSA is significantly higher in the epilepsy group—35% versus healthy children—7.4%. In refractory epilepsy, 44% children have the diagnosis of OSA, in other form of epilepsy around 31% [32, 33]. It is especially important for clinicians, who frequently under-recognize and misinterpret sleep disorders in epilepsy patients.

3. Melatonin secretion in epilepsy

The dynamics of melatonin secretion in epileptic subjects is more complex compared to healthy subjects. Though it appears that human seizure occurrence may have 24-h rhythmicity (and such rhythmicity has also been shown in animals), but there is still no answer to the question on the relationship between the occurrence of seizures and the human circadian rhythm. Many studies on epilepsy have examined the processes that have circadian variation, like hormones secretion, body temperature changes, activity, sleep, and wakefulness, and it is obvious that circadian rhythm and epilepsy at least interact. Unfortunately, there are considerable gaps in the knowledge of such interaction, especially in humans [34].

In epilepsy, melatonin secretion may be disturbed: higher nocturnal melatonin concentrations, a higher melatonin concentration after seizures, or loss/shift of the characteristic diurnal rhythm of secretion are reported by some authors [35–40], while other authors found low baseline levels [41, 42]. Melatonin concentration in patients with epilepsy is sometimes claimed to be slightly increased or unchanged as compared to normal values [38, 43].

However, we observed a statistical dependence between melatonin release amplitude and the number of seizures in different time intervals in the epilepsy of children. Moreover, the time since last seizure has a significant effect on the secretion of melatonin. It should be noted that antiepileptic treatment itself may affect melatonin secretion, which, in fact, was seen in our studies [35, 42]. On the contrary, Dabak et al. showed lower post-seizure melatonin levels in the patients with febrile and afebrile seizures [43]. On the other hand, a normal plasma melatonin curve in epilepsy patients under dim-lit conditions [25] as well as in the study involving epileptic children was found [4].

There is also no agreement between the animal models and the results obtained in the human studies. In animal studies, the data suggest anticonvulsant properties of melatonin, whereas in human studies, it is difficult to reach unambiguous conclusions.

Having in mind the heterogeneity of melatonin secretion and the mode of action in children with epilepsy, Praninskiene et al. postulated that probably not only peripheral melatonin levels but also measurements of melatonin receptors in the brain and melatonin level in central components may be of value [44, 45].

4. Melatonin supplementation in epilepsy in randomized trials

Before the era of randomized trials with melatonin, we witnessed the add-on melatonin supplementation in a few described trials by Peled et al. (improvement in seizures' frequency in five of six children on 3-mg melatonin add-on therapy) [46], Ross et al. (clinical improvement in seizure control and sleep in 20 of 24 children treated with 2.5–7.5 mg of melatonin add-on therapy) [47], and Molina-Carballo et al. (clinical improvement of one child with refractory myoclonic epilepsy treated with melatonin add-on therapy of 200 mg daily) [48].

The first randomized, double-blind, placebo-controlled trial concerning melatonin in epilepsy was conducted in 2004 by Copolla et al. [49]. A total of 25 participants (with mental retardation and epilepsy) aged 3.6–26 years were randomized to oral synthetic fast release melatonin (an initial dose of 3 mg, possible titration to 9 mg). In 2 of 11 seizure-free patients, epileptic seizures appeared on melatonin supplementation [49]. Among seven patients with not adequately controlled epilepsy, the results were not promising (N = 1 seizure-free, N = 2 partial improvement, N = 2 unchanged, N = 2 increase of seizures) [49].

In the same year, Gupta et al. assessed the effect of melatonin add-on supplementation in children with epilepsy aged 3–12 years on carbamazepine or valproic acid monotherapy using the parental questionnaire (Sleep Behavior Questionnaire) [50–54]. In these studies, the children were seizure-free for at least 6 months before the first visit; that is why the authors could not report the influence of melatonin on seizures' frequency [50, 51].

In 2005, Hancock et al. in the next randomized, double-blind, crossover trial evaluated melatonin supplementation (two dose regimen: 5 or 10 mg) in 8 patients aged 18 months to 31 years with epilepsy and tuberous sclerosis complex [55, 56]. During the study period of 6 months, no change in seizure frequency was noted at either dose [55, 56].

Goldberg-Stern et al. conducted another trial investigating response to melatonin (10 mg) in 10 patients with a refractory epilepsy aged 9–32 years (N = generalized epilepsy, N = focal epilepsy) [57]. The mean seizure frequency was 7.75 per day on placebo and 4.6 on melatonin treatment [57]. The limitation of this study was the absence of dim light melatonin-onset measurement.

The randomized double-blind placebo-controlled trial performed by Jain et al. showed that a 9-mg sustained release melatonin formulation decreased sleep latency and wakefulness after sleep onset (WASO) as compared to placebo [58]. This group consisted of 10 children aged 6–11 years diagnosed with epilepsy (focal epilepsy N = 6, generalized epilepsy-childhood absence epilepsy N = 3, undetermined N = 1) with intelligence quotient (IQ) > 70 [58]. Melatonin was given for 30 min before bedtime for 9 weeks. Apart from melatonin, children received different antiepileptic drugs as monotherapy: zonisamide, lamotrigine, levetiracetam, oxcarbazepine, and carbamazepine. According to the authors of the study, no worsening in seizures frequency was observed. Eight participants remained seizure-free, and another two experienced 50% reduction in seizure frequency on melatonin treatment.

Elkhayat et al. in a group of 23 children with refractory epilepsy and in 14 children with controlled seizures (aged 2–15 years) measured melatonin level and assessed the sleep parameters before and after melatonin supplementation (melatonin dose of 1.5–3 mg daily) [59]. The most frequent antiepileptic drug was valproic acid (in intractable epilepsy in 78.2% of patients, in controlled seizures group—85.7%) [59]. After 3 months of melatonin therapy, children with intractable epilepsy experienced improvement in sleep continuity (bedtime resistance, sleep duration, sleep latency, frequent nocturnal arousals, and excessive daytime sleepiness), sleep apnea, nocturnal enuresis, sleep walking, forcible teeth grinding, and Epworth sleepiness score. Melatonin diurnal secretion and the frequency of seizures in controlled seizures group and refractory epilepsy did not differ significantly. Some children experience a decreased severity of seizures.

There are some significant limitation of the abovementioned studies like the small sample size and lack of the homogeneity of the sample: diversity of the epilepsy syndromes, different etiology of seizures, different seizure types, and short period of observation. But treating epilepsy with antiepileptic drugs may also improve sleep architecture and restore sleep cycle. The very limited number of randomized studies did not allow to draw definite conclusions about melatonin add-on therapy and influence of the treatment on epileptic seizures.

5. Melatonin in attention-deficit/hyperactivity disorder (ADHD)

About 25–50% of children with ADHD experience sleep problems [60]. The frequency of sleep problems is almost two-fold higher in a case of stimulant treatment. Sleep disturbances are included among diagnostic criteria for ADHD in the DSM third edition.

Miano et al. distinguished five sleep phenotypes in ADHD [61, 62]:

1. phenotype related to hypoarousal state, primary form of ADHD;
2. phenotype related to delayed sleep phase syndrome;
3. phenotype related to sleep-disordered breathing (SDB) from snoring to obstructive sleep apnea;
4. phenotype related to restless leg syndrome and/or periodic limb movements;
5. phenotype related to sleep epilepsy and/or EEG interictal epileptic discharges.

The most common complaint is sleep-onset insomnia, and rarely, sleep problems are related to a delayed sleep phase syndrome. Also, SDB is highly associated with disturbed attention and hyperactivity, and children with SDB are more sensitive to oxidative stress [61–63].

Based on trials conducted in this population, melatonin treatment in doses ranging between 3 and 6 mg/day may reduce sleep-onset delay and increased sleep duration time [61–63].

6. Melatonin in autism spectrum disorders (ASDs)

Autistic spectrum disorders are frequently connected with sleep disturbances (30–53% or up to 50–80%) [64, 65]. The most common medication used in sleep difficulties is melatonin, apart from behavioral interventions.

In children with autistic spectrum disorders, melatonin levels are lower [65–67] or within normal values [64, 68, 69]. Based on parental questionnaires and clinician completed forms of 1518 ASD children aged 4–10 years, Braam et al. informed about a much higher percentage of sleep problems in ASD (71%) and a higher necessity of drug intake (>46% children on more than one drug promoting sleep) [29]. In the latest double-blind study conducted by Gringras et al., 125 ASD children (among them 3.2% children with the diagnosis of Smith-Magenis syndrome (SMS)) received prolonged-release melatonin or placebo for 13 weeks [70]. Melatonin treatment prolonged the total sleep time (melatonin 57.5 min vs. placebo 9.14 min) and decreased sleep latency (melatonin 39.6 min vs. placebo 12.5 min) [70]. Veatch et al. studied the possible genetic background of sleep problems in ASD by evaluation of two melatonin pathway genes: acetylserotonin O-methyltransferase (ASMT) and cytochrome P450 1A2 (CYP1A2) [68]. The authors found a higher prevalence of variants responsible for a decreased expression of ASMT and a lower CYP1A2 enzyme activity [68]. On the other hand, a lower CYP1A2 enzyme activity may be responsible for slow metabolism and the possibility of lack of efficacy of exogenous melatonin with time. That is why some children may benefit from low melatonin dose like 0.5 mg rather than higher (exceeding 5–6 mg) [64, 65, 71, 72].

Some authors speculate that melatonin as a hormone derived from serotonin may be of a special interest in autism neurobiology [73]. Another interesting finding is that melatonin levels may be negatively correlated with the severity of autistic features. This assumption was made by the examination of sulfatoxymelatonin level in urine of 60 mothers of a child with ASD features and in control group.

A few RDBPC trials showed that melatonin may improve communication [74] and anxiety in children with ASD [75]. Based on the knowledge from placebo-controlled studies, long-acting melatonin preparations at bedtime improve the sleep latency and the total sleep time [67, 69, 70, 74, 76–80].

7. Melatonin in other neurodevelopmental disabilities (NDDs)

Reported prevalence of sleep disturbances in children with neurodevelopmental disabilities is up to 86% [81]. An interesting double-masked randomized placebo-controlled phase III trial was performed by Gringras et al. One hundred and forty-six children aged 3–15 years were treated with melatonin (0.5–12 mg) or placebo for 12 weeks [82]. In melatonin-treated group, the total sleep time increased by 23 min and sleep latency was reduced by around 38 min [82].

Melatonin may be affective in sleep problems in many genetic syndromes, especially in Angelman syndrome (AS), Smith-Magenis syndrome (SMS), Rett syndrome (RS), San Filippo syndrome, and tuberous sclerosis complex syndrome (TSCS) [83–90]. In these genetic conditions, sleep problems are one of the phenotype features. Sleep apnea is a frequent finding in children with Down syndrome and with Prader-Willi syndrome [83–91].

The results of Hancock et al. on the urinal 6-sulfatoxymelatonin excretion in seven TSCS patients revealed, however, no evidence of abnormal excretion of melatonin in patients with tuberous sclerosis complex and sleep disorder [55, 56, 83, 92]. All but one of the patients showed a normal circadian rhythm of melatonin secretion. However, the authors were aware that a small number of analyzed cases weakened their reasoning. Our investigations suggest that not only disordered sleep but also the shift of melatonin secretion may be expected in TSCS children with frequent seizures [88]. We also noticed that melatonin profiles are not homogeneous in TSCS patients [88]. Unfortunately, both researchers supposition are based on the results gathered from a small TSCS group.

Children with Angelman syndrome may present with sleep-onset insomnia as well as sleep maintenance problems, and low endogenous melatonin levels are often claimed to be an essential feature of melatonin secretion in their circadian rhythms [83–90]. Our studies with mathematical modeling of melatonin secretion showed that the phase parameters of melatonin cycle (DMLO parameters, phase or duration of melatonin amplitude) could be the key characteristic of AS children [87].

The recommended melatonin dose in Angelman syndrome is very small like 0.3–0.5 mg, because of the high prevalence of slow melatonin metabolizers [90]. In TSCS, a decreased sleep total time and multiple awakenings are evident; the recommended dose of melatonin is 5–10 mg. Melatonin may reduce the sleep problems (the frequent awakenings) in Rett syndrome in the daily dose of 2.5–7.5 mg [83–85, 92]. Children with SMS have an early sleep onset (19.30–20.30), repeated and prolonged walking at night, and an early sleep offset (04:00–05.00) [91].

Because of inverted melatonin circadian profile, a complex but promising treatment was found: a combination of acebutolol in the morning (10 mg/kg decrease melatonin level during the day) and melatonin in the evening [91].

During the conference in Rome in 2014, Bruni et al. postulated recommendation for melatonin treatment guidelines in children with neurodevelopmental disabilities and insomnia [15]:

1. no age limit (safe administration >6 months of age),
2. if used as a chronobiotic 3–4 hs before bedtime (if used as a sleep inductor 30 min before sleep time) with starting dose 0.2–0.5 mg (titrated by 0.2–0.5 mg every week till maximum dose of 3 (<40 kg) and 5 mg (>40 kg),
3. treatment duration should not be <1 month, therapy adjusted to the patient; if normal sleep cycle is restored 1 week without melatonin treatment, once a year is recommended (especially during summer).

8. Melatonin in hypoxic-ischemic brain injury

During the last decade, melatonin has started to be considered as an attractive option in order to minimize the neurological sequelae from hypoxic-ischemic brain injury [93–95]. The brain itself is particularly sensitive to free radicals damage due to its high utilization of oxygen, its relatively poorly developed antioxidant defense, and its high amount of easily oxidizable fatty acids. Melatonin may serve as a potential therapeutic free radical scavenger (hydroxyl radicals, hydrogen peroxide, singlet oxygen) and broad-spectrum antioxidant (upregulation of antioxidant pathways: superoxide dismutase, glutathione, catalase, glutathione peroxidase, glutathione reductase) [96–98]. Based on experimental studies, melatonin may increase the number of neurons in the CA1, CA2–CA3 areas and dentate gyrus of the hippocampus and parietal cortex, reduce the expression of the glial fibrillary acidic protein, and regulate the expression of myelin basic protein and oligodendrocytes' function (regulation of myelination process) [96–98].

Aly et al. examined the effect of melatonin on clinical, biochemical, neurophysiological, and radiological outcomes of neonates with hypoxic-ischemic encephalopathy (HIE) [99]. They performed a prospective trial involving 45 newborns randomized in the hypothermia alone and hypothermia and melatonin groups. All infants were studied with repeated EEG and brain MRI. In all patients, superoxide dismutase (SOD) and nitric oxide (NO) were measured. These examinations showed an increased melatonin and a decreased NO in the hypothermia-melatonin group [99]. Because of postulated unpredicted bioavailability of oral melatonin, Merchant et al. gave blood transfusion of 0.04–0.6 µg/kg melatonin to 18 preterm babies (less than 31 weeks gestation, less than 7 days old) for 2 h [100]. As a result they found melatonin concentration peak similar to adults. Another challenge might be the possibility to administer melatonin antenatally, in order to prevent or reduce brain hypoxic insult in preterm babies

[94]. Denihan et al. employed untargeted metabolomics to identify metabolomic biomarkers of umbilical cord blood after hypoxic injury [101]. The analysis was performed using direct injection FT-ICR mass spectrometry. Some metabolites allowed for differentiation between children with perinatal asphyxia with recovery and children with perinatal asphyxia followed by hypoxic-ischemic encephalopathy like melatonin leucine, kynurenine, and 3-hydroxydo-decanoic acid. HIE itself was associated with abnormalities in tryptophan and pyrimidine metabolism.

Children after hypoxia-ischemia brain injury often develop circadian rhythm disorders. Yang et al. documented that in experimental studies, mRNA and protein expression of pineal arylalkylamine N-acetyltransferase (AANAT) and melatonin are impaired after hypoxic damage [102]. They postulated that miR-325-3p (micro RNA) may play a role of potential down-regulator of AANAT-rate-limiting enzyme for melatonin synthesis [102].

9. Conclusions

Melatonin may be effective not only in primary sleep disorders but also in some above-mentioned neurological disorders in children. In adults, postulated antioxidative potential of melatonin may be of value in neurodegenerative diseases like Parkinson, Alzheimer, and Huntington's disease [98].

Because disturbed circadian rhythms and poor sleep quality are associated with increased risks of cardiovascular, metabolic, and cognitive diseases, poor quality of life, and even with mortality, exogenously administered melatonin is often claimed to be a remedy for all these problems. However, many conflicting results obtained in various areas of research on the functions and roles of melatonin require caution and the extension of basic research [103–108]. First of all further standardized studies of the human circadian rhythm and of its disturbances affecting melatonin rhythms by interfering with its production and secretion are necessary, as well as the studies of the interaction between circadian rhythm and seizures in animal models. Moreover, the melatonin role in epilepsy and the effects of antiepileptic drug treatment (in relation to the circadian rhythm phases) should be explored. As concerning exogenous melatonin application, larger study groups are required to identify proper therapeutic dosage regarding age, concrete disease, and to check the clinical efficacy of melatonin add-on therapy.

Filling up the gaps in the knowledge about the interactions of circadian rhythm, human epilepsy, and melatonin will improve our understanding of the undergoing processes and the patients' treatment quality.

Conflict of interest

The authors declare no conflict of interest.

Author details

Justyna Paprocka^{1*}, Marek Kijonka² and Maria Sokół²

*Address all correspondence to: justyna.paprocka@interia.pl

1 Department of Child Neurology, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland

2 Department of Medical Physics, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland

References

- [1] Lack L, Wright HR. Chronobiology of sleep in humans. *CMLS*. 2007;**64**:1205-1215
- [2] Barnard AR, Nolan PM. When clocks go bad: Neurobehavioural consequences of disrupted circadian timing. *PLoS Genetics*. 2008;**30**:1-8
- [3] Tordjman S, Chokron S, Delorme R, Charrier A, Bellissant E, Jaafari N, Fougere C. Melatonin: Pharmacology, functions and therapeutic benefits. *Current Neuropharmacology*. 2017;**15**:434-443
- [4] Brzezinski A. Melatonin in humans. *The New England Journal of Medicine*. 1997;**336**:186-195
- [5] Lewy AJ, Sack RL, Blood ML, Bauer VK, Cutler NL, Thomas KH. Melatonin marks circadian phase position and resets the endogenous circadian pacemaker in humans. *Ciba Foundation Symposium*. 1995;**183**:303e17 [discussion 317e21]
- [6] Zisapel N. New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. *British Journal of Pharmacology*. 2018. DOI: 10.1111/bph.14116
- [7] Lewy AJ, Sack RL, Singer CM. Immediate and delayed effects of bright light on human melatonin production: Shifting “dawn” and “dusk” shifts the dim light melatonin onset (DLMO). *Annals of the New York Academy of Sciences*. 1985;**453**:253-259
- [8] Lewy AJ, Sack RL. The dim light melatonin onset as a marker for circadian phase position. *Chronobiology International*. 1989;**6**:93-102
- [9] Mandrell BN, Avent Y, Walker B, Loew M, Tynes BL, Crabtree VM. In home salivary melatonin collection: Methodology for children and adolescents. *Developmental Psychobiology*. 2018;**60**:118-122
- [10] Keijzer H, Smits MG, Peeters T, Looman CW, Endenburg SC, Gunnewiek JM. Evaluation of salivary melatonin measurements for dim Light Melatonin onset calculations in patients with possible sleep-wake rhythm disorders. *Clinica Chimica Acta*. 2011;**17**:417-418

- [11] Tchekalarova J, Moyanova S, De Fusco A, Ngomba RT. The role of the melatonergic system in epilepsy and comorbid psychiatric disorders. *Brain Research Bulletin*. 2015; **119**:80-92
- [12] Stewart LS. Endogenous melatonin and epileptogenesis: Facts and hypothesis. *The International Journal of Neuroscience*. 2001; **107**:77-85
- [13] Steward LS, Leung LS. Hippocampal melatonin receptors modulate the seizure threshold. *Epilepsia*. 2005; **46**:473-480
- [14] Reiter R, Tan DX, Rosales-Corral S, Galano A, Zhou XJ, Xu B. Mitochondria: Central organelles for melatonin's antioxidant and anti-aging actions. *Molecules*. 2018; **23**:509. DOI: 10.3390/molecules23020509
- [15] Bruni O, Alonso-Alconada D, Besag F, Biran V, Braam W, Cortese S, Mooavero R, Parisi P, Smits M, van der Heijden K, Curatolo P. Current role of melatonin in pediatric neurology: Clinical recommendations. *European Journal of Paediatric Neurology*. 2015; **19**:122-133
- [16] Hofstra WAE, de Weerd AW. The circadian rhythm and its interaction with human epilepsy: a review of literature. *Sleep Medicine Reviews*. 2009; **13**:413-420
- [17] Van Golde E, Gutter T, de Weerd AW. Sleep disturbances in people with epilepsy: Prevalence, impact and treatment. *Sleep Medicine Reviews*. 2011; **15**:357-368
- [18] Derry CP, Duncan S. Sleep and epilepsy. *Epilepsy & Behavior*. 2013; **26**:394-404
- [19] Minecan D, Natarajan A, Marzec M, Malow B. Relationship of epileptic seizures to sleep stage and sleep depth. *Sleep*. 2002; **25**:899-904
- [20] Foldvary-Schaefer N, Grigg-Damberg M. Sleep and epilepsy: What we know, don't know, and need to know. *Journal of Clinical Neurophysiology*. 2006; **23**:4-20
- [21] Herman JH. Circadian rhythm disorders in pediatrics. *Pediatric Annals*. 2008; **37**:488-495
- [22] Herman ST, Walczak TS, Bazil CW. Distribution of partial seizures during the sleep-wake cycle: Differences by seizures onset site. *Neurology*. 2001; **56**:1453-1459
- [23] Jain SV, Kothare SV. Sleep and epilepsy. *Seminars in Pediatric Neurology*. 2015; **22**:86-92
- [24] Hofstra WA, Grootemarsink BE, Dieker R, van der Palen J, de Weerd AW. Temporal distribution of clinical seizures over 24-hour day: A retrospective observational study in tertiary epilepsy clinic. *Epilepsia*. 2009; **50**:2019-2026
- [25] Pavlova MK, Shea SA, Scheer FAJL, Bromfield EB. Is there a circadian variation of epileptiform abnormalities in idiopathic generalized epilepsy? *Epilepsy & Behavior*. 2009; **16**: 461-467
- [26] Gogou M, Haidopoulou K, Eboriadou M, Pavlidou E, Hatzistylianou M, Pavlou E. Sleep respiratory parameters in children with idiopathic epilepsy: A cross-sectional study. *Epilepsy Research*. 2016; **126**:10-15

- [27] Monteleone P, Tortorella A, Borriello R, Natale M, Cassandro P, Maj M. Suppression of nocturnal plasma melatonin levels by evening administration of sodium valproate in healthy humans. *Biological Psychiatry*. 1997;**41**:336-341
- [28] Braam W, Smits MG, Didden R, Korzilius H, Van Geijlswijk I, Curfs LMG. Exogenous melatonin for sleep problems in individuals with intellectual disability: a meta-analysis. *Developmental Medicine and Child Neurology*. 2009;**51**:340-349
- [29] Braam W, Ehrhart F, Maas APHM, Smits MG, Curfs L. Low maternal melatonin level increases autism spectrum disorder risk in children. *Research in Developmental Disabilities*. 2018 Feb 28. DOI: 10.1016/j.ridd.2018.02.017
- [30] Takaesu Y, Futenma K, Kobayashi M, Komada Y, Tanaka N, Yamashina A, Inoue Y. A preliminary study on the relationships between diurnal melatonin secretion profile and sleep variables in patients emergently admitted to the coronary care unit. *Chronobiology International*. 2015;**32**:875-879
- [31] Bazil CW. Effects of antiepileptic drugs on sleep structure: Are the drugs equal? *CNS Drugs*. 2003;**17**:719-728
- [32] Urquhart DS, Kehinde OO, Mclellan AE. Observational pilot study of reported symptoms of obstructive sleep apnoea in children with epilepsy. *Developmental Medicine and Child Neurology*. 2016;**58**:1063-1068
- [33] Accardo JA, Malow BA. Sleep, epilepsy, and autism. *Epilepsy & Behavior*. 2015;**47**:202-206
- [34] Wytske A, Hofstra WAE, de Weerd AW. How to access the circadian rhythm in humans: A review of the literature. *Epilepsy & Behavior*. 2008;**13**:438-444
- [35] Paprocka J, Rec R, Marszał E. Melatonin and childhood refractory epilepsy- a pilot study. *Medical Science Monitor*. 2010;**16**:CR389-CR396
- [36] Paprocka J, Marszał E. Melatonina w neurologii. *Klinika Pediatryczna*. 2007;**15**:432-437
- [37] Schapel GJ, Beran RG, Kennaway DL, McLoughney J, Matthews CD. Melatonin response in active epilepsy. *Epilepsia*. 1995;**36**:75-78
- [38] Molina-Carballo A, Munoz-Hoyos A, Rodriguez-Cabezas T, Acuña-Castroviejo D. Day-night variations in melatonin secretion by the pineal gland during febrile and epileptic convulsions in children. *Psychiatry Research*. 1994;**52**:273-283
- [39] Molina-Carballo A, Munoz-Hoyos A, Sanchez-Forte M, Uberoz-Fernandez J, Moreno-Madrid F, Acuna-Castroviejo D. Melatonin increases following convulsive seizures may be related to its anticonvulsant properties at physiological concentrations. *Neuropediatrics*. 2007;**38**:122-125
- [40] Waldhauser F, Kovács J, Reiter E. Age-related changes in melatonin levels in humans and its potential consequences for sleep disorders. *Experimental Gerontology*. 1998;**33**:759-772
- [41] Bazil CW, Short D, Crispin D, Zheng W. Patients with intractable epilepsy have low melatonin, which increases following seizures. *Neurology*. 2000;**55**:1746-1748

- [42] Paprocka J, Kijonka M, Pecka M, Sokół M. Melatonin in Epilepsy: A New Mathematical Model of Diurnal Secretion. *International Journal of Endocrinology*. 2016;**2016**:3861461. DOI: 10.1155/2016/3861461
- [43] Dabak O, Altun D, Arslan M, Yaman H, Vurucu S, Yesilkaya E, Unay B. Evaluation of plasma melatonin levels in children with afebrile and febrile seizures. *Pediatric Neurology*. 2016;**57**:51-55
- [44] Praninskiene R, Dumalakienė I, Kemezys R, Mauricas M, Jucaite A. Melatonin secretion in children with epilepsy. *Epilepsy & Behavior*. 2012;**25**:315-322
- [45] Praninskiene R, Dumalakienė I, Kemezys R, Mauricas M, Jucaite A. Diurnal melatonin patterns in children: Ready to apply in clinical practice? *Pediatric Neurology*. 2012;**46**:70-76
- [46] Peled N, Shorer Z, Peled R, Pillar G. Melatonin effect on seizures in children with severe neurologic deficit disorders. *Epilepsia*. 2001;**43**:1208-1210
- [47] Ross C, Davies P, Whitehouse W. Ross Melatonin treatment for sleep disorders in children with neurodevelopmental disorders: An observational study. *Developmental Medicine and Child Neurology*. 2002;**44**:339-344
- [48] Molina-Carballo A, Muñoz-Hoyos A, Reiter RJ, Sánchez-Forte M, Moreno-Madrid F, Rufo-Campos M, Molina-Font JA, Acuña-Castroviejo D. Utility of high doses of melatonin as adjunctive anticonvulsant therapy in a child with severe myoclonic epilepsy: Two years' experience. *Journal of Pineal Research*. 1997;**23**:97-105
- [49] Coppola G, Iervolino G, Mastrosimone M, La Torre G, Ruiu F, Pascotto A. Melatonin in wake-sleep disorders in children, adolescents and young adults with mental retardation with or without epilepsy: A double-blind, crossover, placebo-controlled trial. *Brain & Development*. 2004;**26**:373-376
- [50] Gupta M, Gupta YK, Anieja AS, Kohli K. Effects of add-on melatonin on sleep in epileptic children on carbamazepine monotherapy: A randomized placebo controlled trial. *Sleep and Biological Rhythms*. 2004;**2**:215-219
- [51] Gupta M, Anieja S, Kohli K. Add-on melatonin improves quality of life in epileptic children on valproate monotherapy: a randomized, double-blind, placebo-controlled trial. *Epilepsy & Behavior*. 2004;**5**:316-321
- [52] Gupta M, Gupta YK, Agarwal S, Anieja S, Kalaivani M, Kohli K. Effects of add-on melatonin administration on antioxidant enzymes in children with epilepsy taking carbamazepine monotherapy: A randomized, double-blind, placebo-controlled trial. *Epilepsia*. 2004;**45**:1636-1639
- [53] Gupta M, Kohli K, Gupta YK. Modulation of serum concentrations of melatonin by carbamazepine and valproate. *Indian Journal of Physiology and Pharmacology*. 2006;**50**:79-82

- [54] Gupta M, Anieja S, Kohli K. Add-on melatonin improves sleep behavior in children with epilepsy: Randomized, double-blind, placebo-controlled trial. *Journal of Child Neurology*. 2005;**20**:112-115
- [55] Hancock E, O'Callaghan F, English J, Osborne JP. Melatonin excretion in normal children and in tuberous sclerosis complex with sleep disorder responsive to melatonin. *Journal of Child Neurology*. 2005;**20**:21-25
- [56] Hancock E, O'Callaghan F, Osborne JP. Effect of melatonin dosage on sleep disorder in tuberous sclerosis complex. *Journal of Child Neurology*. 2005;**20**:78-80
- [57] Goldberg-Stern H, Oren H, Peled N, Garty BZ. Effect of melatonin of seizures frequency in intractable epilepsy: A pilot study. *Journal of Child Neurology*. 2012;**27**:1524-1528
- [58] Jain SV, Horn PS, Simakajornboon N, Beebe DW, Holland K, Byars AW, Glauser TA. Melatonin improves sleep in children with epilepsy: A randomized, double-blind cross-over study. *Sleep Medicine*. 2015;**16**:637-644
- [59] Elkhayat HA, Hassanein SM, Tomoum HY, Abd-Elhamid IA, Asaad T, Elwakkad AS. Melatonin and sleep-related problems in children with intractable epilepsy. *Pediatric Neurology*. 2010;**42**:250-254
- [60] Cortese S, Brown TE, Corkum P, Gruber R, O'Brien LM, Stein M, Weiss M, Owens J. Assessment and management of sleep problems in youths with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2013;**52**:784-796
- [61] Miano S, Parisi P, Villa MP. The sleep phenotypes of attention deficit hyperactivity disorder: The role of arousal during sleep and implications for treatment. *Medical Hypotheses*. 2012;**79**:147-153
- [62] Miano S, Esposito M, Foderaro G, Ramelli GP, Pezzoli V, Manconi M. Sleep-related disorders in children with attention-deficit hyperactivity disorder: Preliminary results of a full sleep assessment study. *CNS Neuroscience & Therapeutics*. 2016;**22**:906-914
- [63] Um YH, Hong S-C, Jeong J-H. Sleep problems as predictors in attention-deficit hyperactivity disorders: Causal mechanisms, consequences and treatment. *Clinical Psychopharmacology and Neuroscience*. 2017;**15**:9-18
- [64] Goldman SE, Adkins KW, Calcutt MW, Carter MD, Goodpaster RL, Wang L, Shi Y, Burgess HJ, Hachey DL, Malow BA. Melatonin in children with autism spectrum disorders, endogenous and pharmacokinetic profiles in relation to sleep. *Journal of Autism and Developmental Disorders*. 2014;**44**:2525-2535
- [65] Liu X, Hubbard JA, Fabes RA, Adam JB. Sleep disturbances and correlates of children with autism spectrum problems. *Child Psychiatry and Human Development*. 2006;**37**: 179-1991

- [66] Krakowiak P, Goodlin-Jones B, Hertz-Picciotto I, Croen LA, Hansen RI. Sleep problems in children with autism spectrum disorders, developmental delays, and typical development: A population-based study. *Journal of Sleep Research*. 2008;**17**:197-206
- [67] Tordjman S, Najjar I, Bellissant E, Anderson GM, Barbueroth M, Cohen D, Jaafari N, Schischmanoff O, et al. Advances in the research of melatonin in autism spectrum disorders. *International Journal of Molecular Sciences*. 2013;**14**:20508-20542
- [68] Veatch OJ, Pendergast JS, Allen MJ, Leu RM, Johnson CH, Elsea SH, Malow BA. Genetic variation in melatonin pathway enzymes in children with autism spectrum disorder and comorbid sleep onset delay. *Journal of Autism and Developmental Disorders*. 2015;**45**:100-110
- [69] Veatch OJ, Goldman SE, Adkins KW, Malow BA. Melatonin in children with autism spectrum disorders: how does the evidence fit together? *Journal of Natural Sciences*. 2015;**1**:125
- [70] Gringras P, Nir T, Breddy J, Frydman-Maron A, Findling RL. Efficacy and safety of pediatric prolonged-release melatonin form insomnia in children with autism spectrum disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2017;**56**:948-957
- [71] Malow BA. The interaction between sleep and epilepsy. *Epilepsia*. 2007;**48**:36-38
- [72] Jones C, Huyton M, Hindley D. Melatonin and epilepsy. *Archives of Disease in Childhood*. 2005;**90**:1203
- [73] Mazzone L, Postorino V, Siracusano M, Riccioni A, Curatolo P. The relationship between sleep problems, neurobiological alterations, core symptoms of autism spectrum disorder, and psychiatric comorbidities. *Journal of Clinical Medicine*. 2018;**7**:102. DOI: 10.3390/jcm7050102
- [74] Wright B, Sims D, Smart S, Alwazeer A, Alderson-Day B, Allgar V, Whitton C, Tomlinson H, Bennett S, Jardine J, McCaffrey N, Leyland C, Jakeman C, Miles J. Wright Melatonin versus placebo in children with autism spectrum conditions and severe sleep problems not amenable to behaviour management strategies: A randomised controlled crossover trial. *Journal of Autism and Developmental Disorders*. 2001;**41**:175-184
- [75] Wasdell MB, Jan JE, Bomben MM, Freeman RD, Rietveld WJ, Tai J, Hamilton D, Weiss MD. A randomized, placebo-controlled trial of controlled release melatonin treatment of delayed sleep phase syndrome and impaired sleep maintenance in children with neurodevelopmental disabilities. *Journal of Pineal Research*. 2008;**44**:57-64
- [76] Guenole F, Godbout R, Nicolas A, Franco P, Claustrat B, Baleyte JM. Melatonin for disordered sleep in individuals with autism spectrum disorders: Systematic review and discussion. *Sleep Medicine Reviews*. 2011;**15**:379-387
- [77] Hellmer K, Nystrom P. Infant acetylcholine, dopamine, and melatonin dysregulation: Neonatal biomarkers and causal factors for ASD and ADHD phenotypes. *Medical Hypotheses*. 2017;**100**:64-66

- [78] Kotagal S, Broomall E. Sleep in children with autism spectrum disorder. *Pediatric Neurology*. 2012;**47**:242-251
- [79] Andersen IM, Kaczmarek J, McGrew SG, Malow BA. Melatonin for insomnia in children with autism spectrum disorders. *Journal of Child Neurology*. 2008;**23**:482-485
- [80] Cuomo BM, Vaz S, Lee EAL, Thompson C, Rogerson JM, Falkmer T. Effectiveness of sleep-based interventions for children with autism spectrum disorder: A meta-synthesis. *Pharmacotherapy*. 2017;**37**:555-578
- [81] Robinson-Shelton A, Malow BA. Sleep disturbances in neurodevelopmental disorders. *Current Psychiatry Reports*. 2016;**18**:6
- [82] Gringras P, Gamble C, Jones AP, Wiggs ML, Williamson PR, Sutcliffe A, Montgomery P, Whitehouse WP, Choonara I, Allport T, Edmond A, Appleton R, MENDS Study Group. Melatonin for sleep problems in children with neurodevelopmental disorders: Randomized double masked placebo controlled trial. *BMJ*. 2012;**345**:6664
- [83] Schwichtenberg AJ, Malow BA. Melatonin treatment in children with developmental disabilities. *Sleep Medicine Clinics*. 2015;**10**:181-187
- [84] Checa-Ros A, Munoz-Gallego A, Munoz-Gallego M, Molina-Carballo A, Narbona-Galdo S, Jerez-Calero A, Augustin-Morales MDC, Munoz-Hoyos A. Clinical considerations derived from the administration of melatonin to children with sleep disorders. *Pediatric Neurology*. 2018;**78**:61-69
- [85] Appleton RE, Jones AP, Gamble C. The use of melatonin in children with neurodevelopmental disorders: Randomized double masked placebo controlled, parallel study (MENDS). *Health and Technology Access*. 2012;**16**:1-239
- [86] Spruyt K, Braam W, Smits M, Curfs LMG. Sleep complaints and the 24-h melatonin level in individuals with Smith-Magenis syndrome: Assessment for effective intervention. *CNS Neuroscience & Therapeutics*. 2016;**22**:928-935
- [87] Paprocka J, Kijonka M, Wojcieszek P, Pęcka M, Emich-Widera E, Sokół M. Melatonin and Angelman syndrome – implications and mathematical model of diurnal secretion. *International Journal of Endocrinology*. 2017;**(2017)**, Article ID 5853167. DOI: 10.1155/2017/5853167
- [88] Paprocka J, Kijonka M, Boguszewicz Ł, Sokół M. Melatonin in Tuberous Sclerosis Complex Analysis Using Modern Mathematical Modeling Methods. *International Journal of Endocrinology*. 2017;**2017**:8234502. DOI: 10.1155/2017/8234502
- [89] Sheldon S. Proconvulsant effects of oral melatonin in neurologically disabled children. *Lancet*. 1988;**351**:1254
- [90] Takaesu Y, Komada Y, Inoue Y. Melatonin profile and its relationship to circadian rhythm sleep disorders in Angelman syndrome patients. *Sleep Medicine*. 2002;**13**:1164-1170
- [91] Spruyt K, Braam W, Smits M, Curfs LMG. Sleep complaints and the 24-h melatonin level in individuals with Smith-Magenis syndrome: Assessment for effective intervention. *CNS Neuroscience & Therapeutics*. 2016;**22**:928-935

- [92] Bruni O, Angriman M, Calisti F, Comandini A, Esposito G, Cortese S, Ferri R. Practitioner review: Treatment of chronic insomnia in children and adolescent with neurodevelopmental disabilities. *The Journal of Child Psychology and Psychiatry*. 2018;**59**:489-508
- [93] Alonso-Alconada D, Alvarez A, Martinez-Ibarguen A, Hilario E. Neuroprotective effect of melatonin: A novel therapy against perinatal hypoxia-ischemia. *International Journal of Molecular Sciences*. 2013;**14**:9379-9395
- [94] Biran V, Phan Duy A, Decobert F, Bednarek N, Alberti C, Baud O. Is melatonin ready to be used in preterm infants as a neuroprotectant? *Developmental Medicine and Child Neurology*. 2014;**56**:717-723
- [95] Hendaus M, Jamha FA, Alhammadi A. Melatonin in the management of perinatal hypoxic-ischemic encephalopathy: Light at the end of the tunnel? *Neuropsychiatric Disease and Treatment*. 2016;**12**:2473-2479
- [96] Hassell KJ, Ezzati M, Alonso-Alconada D, Hausenloy D, Robertson NJ. New horizons for newborn brain protection: Enhancing endogenous neuroprotection. *Archives of Disease in Childhood. Fetal and Neonatal Edition*. 2015;**100**:F541-F552
- [97] Martinello K, Hart AR, Yap S, Mitra S, Robertson NJ. Management and investigation of neonatal encephalopathy: 2017 update. *Archives of Disease in Childhood. Fetal and Neonatal Edition*. 2017;**102**:F346-F358
- [98] Muller AJ, Marks JD. Hypoxic ischemic brain injury: Potential therapeutic interventions for the future. *NeoReviews*. 2014;**15**:177-186
- [99] Aly H, Elmahdy H, El-Dib M, Rowisha M, Awny M, El-Gohary T, Elbatch M, Hamisa M, El-Mashad AR. Melatonin use for neuroprotection in perinatal asphyxia: A randomized controlled pilot study. *Journal of Perinatology*. 2015;**35**:186-191
- [100] Merchant NM, Azzopardi DV, Hawwa AF, McElnay JC, Middleton B, Arendt J, Arichi T, Gressens P, Edwards AD. Pharmacokinetics of melatonin in preterm infants. *British Journal of Clinical Pharmacology*. 2013;**76**:725-733
- [101] Deniham NM, Kirwan JA, Walsh BH, Dunn WB, Broadhurst DI, Boylan B, Murray DM. Untargeted metabolomic analysis and pathway discovery in perinatal asphyxia and hypoxic-ischaemic encephalopathy. *JCBFM*. 2017:1-16
- [102] Yang Y, Sun B, Huang J, Xu L, Pan J, Fang C, Li M, Li G, Tao J, Xang X, Wu Y, Miao P, Wang Y, Li H, Ren Y, Zhan M, Fang Y, Feng X, Ding X. Up-regulation of miR-325-3p suppresses pineal aralkylamine N-acetyltransferase (Aanat) after neonatal hypoxia-ischemia brain injury in rats. *Brain Research*. 1668;**2017**:28-35
- [103] Yalyn O, Arman F, Erdogan F, Kula M. A comparison of the circadian rhythms and the levels of melatonin in patients with diurnal and nocturnal complex partial seizures. *Epilepsy & Behavior*. 2006;**8**:542-546
- [104] Ardura J, Anders J, Garmendia JR, Ardura F. Melatonin in epilepsy and febrile seizures. *Journal of Child Neurology*. 2010;**25**:888-891

- [105] Fauteck J, Schmidt H, Lerch A, Kurlemann G, Witkowski W. Melatonin in epilepsy: First results of replacement therapy and first clinical results. *Biological Signals and Receptors*. 1999;**8**:105-110
- [106] Laakso MI, Leinonen L, Haltonen T, Alila A, Heiskala H. Melatonin, cortisol, and body temperature rhythm in Lennox-Gastaut patients with and without circadian rhythm sleep disorders. *Journal of Neurology*. 1993;**240**:410-416
- [107] Rao ML, Stefan H, Bauer J. Epileptic but not psychogenic seizures are accompanied by simultaneous elevation of serum pituitary hormones and cortisol levels. *Neuroendocrinology*. 1989;**49**:33-39
- [108] Uberos J, Augustin-Morales MC, Molina Carballo A, Florido J, Narbona E, Muñoz-Hoyos A. Normalization of the sleep-wake pattern and melatonin and 6-sulphatoxy-melatonin levels after a therapeutic trial with melatonin in children with severe epilepsy. *Journal of Pineal Research*. 2011;**50**:192-196

