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Effects of Circadian Rhythm and Melatonin on Epilepsy Research

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ABSTRACT

A significant amount of clinical and experimental research has been conducted on the treatment of epilepsy, a condition that negatively impacts human health and quality of life. Circadian rhythm refers to vital physiological changes occurring over an approximately 24-hour period, primarily influenced by daylight. Melatonin levels play a crucial role in this mechanism, with its secretion varying throughout the day. This review aims to assess the potential impact of circadian rhythm-related changes in melatonin levels on epilepsy research findings. The PubMed, Google Scholar, and Web of Science databases were used to search for relevant publications. Articles published up to 2025 were included in the review. Melatonin modulates neuronal electrical activity by reducing glutamatergic transmission and increasing GABAergic neurotransmission. In humans, melatonin has been shown to alleviate seizures and to exert positive effects in the treatment of childhood refractory epilepsy. In addition, it has been found to improve physical, emotional, cognitive, and social functions. A significant portion of experimental studies has confirmed the anticonvulsant properties of melatonin. However, several studies have shown that melatonin exerts direct or indirect proconvulsant effects. This review revealed that epilepsy research data sometimes show contradictory results. The seizure parameters tested in these studies, as well as cognitive and behavioral characteristics, may be influenced by daily variations in circadian rhythms. It was concluded that considering circadian rhythms-related variables during the conduct of these studies and basing all modeling and planning on them is essential.

Keywords: Circadian rhythm, epilepsy, learning, memory, melatonin, seizures.

ÖZ

Epilepsi Araştırmalarında Sirkadiyen Ritim ve Melatoninin Etkileri

İnsan sağlığını ve yaşam kalitesini olumsuz yönde etkileyen epilepsi tedavisine yönelik önemli miktarda klinik ve deneysel araştırma yapılmaktadır. Sirkadiyen ritim gün ışığına bağlı olarak yaklaşık 24 saatlik periyottaki bazı vital değişimleri ifade etmektedir. Melatonin seviyesi bu mekanizmanın en önemli rolünü üstlenmekte ve salınımı günün farklı saatlerinde değişkenlik göstermektedir. Bu derleme, sirkadiyen ritme bağlı melatonin seviyesindeki değişimlerin, epilepsi araştırmalarındaki verilere potansiyel etkisini değerlendirmeyi amaçlamaktadır. Yayın araştırmasında PubMed, Google Scholar ve Web of Science veri tabanları kullanıldı. İncelemede 2025'e kadar yayımlanan makaleler dikkate alındı. Melatonin glutamaterjik iletimi azaltarak ve GABA-erjik sinir iletimini artırarak nöronların elektriksel aktivitesini modüle eder. İnsanlarda melatoninin nöbetleri hafiflettiği ve çocukluk çağı dirençli epilepsinin tedavisindeki olumlu etkileri bildirildi. Buna ilaveten fiziksel, duygusal, bilişsel ve sosyal işlevleri de iyileştirdiği tespit edildi. Deneysel çalışmaların önemli bir kısmı melatoninin antikonvülzan özelliklerini doğrulamaktadır. Birkaç çalışmada melatonin doğrudan veya dolaylı prokonvülzan etki gösterdi. Bu inceleme ile epilepsi araştırmalarından elde edilen verilerin bazen birbirleri ile tam zıt yönde olduğu anlaşıldı. Bu araştırmalarda test edilen nöbet parametreleri ile bilişsel ve davranışsal özelliklerin sirkadiyen ritim dediğimiz günlük değişimlerden etkilenebileceği değerlendirildi. Söz konusu çalışmaların yürütülmesi sırasında sirkadiyen ritme bağlı değişkenleri dikkate almanın, tüm modelleme ve planlamanın buna göre yapılmasının zorunluluk olduğu kanaatine varıldı.

Anahtar Kelimeler: Epilepsi, hafıza, öğrenme, melatonin, nöbetler, sirkadiyen ritim.

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INTRODUCTION

Epilepsy is one of the most common diseases worldwide, with 74.5 million cases, one-fifth of which occur in developed countries (Ngugi et al., 2010). It comes from the Greek word "epilambanein" and means "taking possession." (Magiorkinis et al., 2010). The causes of many cases in developed countries remain unknown (Beghi, 2020). Brain injury, stroke, brain tumor, and congenital malformations are among the identified causes (Bhalla et al., 2011). Excessive alcohol consumption is also a cause of epilepsy (Pandolfo, 2011). Epilepsy is caused by abnormal, transient electrical activity of the brain's nerve cells. Underlying mechanisms include oxidative stress, glutamate excitotoxicity, and mitochondrial disorders (Vishnoi et al., 2016). Melatonin may be an additional treatment for epilepsy (Molina-Carballo et al., 1997).

Circadian rhythm is a mechanism that allows organisms to adapt to cyclical changes in their environment (Ouyang et al., 1998; Hut & Beersma 2011). The circadian rhythm is self-sustaining and is derived from the Latin words "circa" and "dies." It is a period of approximately 24 hours (Welsh et al., 1995; Czeisler et al., 1999). Circadian rhythms in single-celled organisms depend solely on genetic mechanisms and stimuli called Zeitgebers (Moore & Lenn 1972). The SCN integrates the information it receives from the retinal ganglion cells with other non-photic temporal cues (Challet & Pévet 2003). In this way, it synchronizes dependent oscillators in other brain regions by generating and maintaining a rhythm (Yamazaki et al., 2000). Light affects retinal ganglion cells and stimulates the SCN. Cells that transmit melanopsin participate in the circadian rhythm (Berson et al., 2002). The SCN regulates melatonin release. This light-triggered system also sends signals to the SCN and other brain regions that regulate sleep (Hughes et al., 2012). The hypothalamus controls hunger, thirst, sleep, body temperature, and some hormones (Cardinali et al., 1998). Melatonin, which is also considered a vitamin when consumed with food, is synthesized in the pineal gland (Tan et al., 2003; Banach et al., 2011; Akyuz et al., 2021).

The human body has a specific balance of temporal distribution. This balance, called the circadian rhythm, must function smoothly for a healthy life. Endogenous melatonin synthesis is crucial for this balance. Disruption of this rhythm due to decreased secretion of melatonin can lead to many diseases. The normal functioning of the epiphysis depends on the rhythmic regulation of the SCN. SCN activity decreases at night compared with that during the day. Melatonin release occurs as SCN activity decreases in the evening. The gradual working order in the hypothalamus forms the circadian rhythm of mammals (Gunata et al., 2020). Disrupted circadian rhythm negatively affects melatonin levels and the health of the elderly (Poeggeler, 2005).

Melatonin has both preventive and therapeutic effects in many diseases, including neurological diseases. Studies have demonstrated the prophylactic and therapeutic effects of melatonin in neurological diseases. Neurologists and administrators must work together to develop melatonin therapy for patients with neurological problems. Melatonin may offer a solution to this problem (Gunata et al., 2020).

Animal studies investigating the relationship between melatonin and epileptogenesis primarily support the anticonvulsant effect hypothesis. However, human studies vary in their design and use small numbers of participants, and the results do not always clearly confirm this hypothesis (Vasileva, 2021).

Current research focuses on the use of melatonin as an adjunct therapy for epilepsy. While some recent randomized controlled trials have shown beneficial results with adjunct melatonin therapy for epilepsy, the validity of these results is not universally accepted for various reasons. Adjunctive melatonin therapy improves sleep onset time and seizure severity in epileptic patients (Liu et al., 2024). Endogenous melatonin levels vary at different times of the day due to the circadian rhythm. This review aims to clarify the potential impact of circadian rhythm and resulting changes in melatonin levels on epilepsy research data.

SEARCH AND SELECTION STRATEGIES

The PubMed, Google Scholar, and Web of Science databases were used to search for articles on the subject. The following keywords are used: epilepsy, experimental epilepsy, seizures, circadian rhythm, melatonin, learning memory, and behavior. The review considered articles published upto and including 2025, as well as older articles that still retain their relevance. We examined 90 articles and books related to rodent epilepsy models. This research focused on the effects of circadian rhythm-related variables on research outcomes.

CIRCADIAN RHYTHM AND MELATONIN

Melatonin may also function as a neurotransmitter through receptor-mediated mechanisms. Melatonin facilitates transmission via ATP-sensitive potassium channels experimental studies have shown that mice lacking the KATP channel subunit are sensitive to hypoxia and have a low seizure threshold (Bal et al., 2018). Melatonin can suppress glutamate-mediated excitation through NMDA glutamatergic receptors, increase GABA concentrations, and increase GABAA receptor sensitivity (Banach et al., 2011). However, endogenous melatonin may inhibit dopaminergic transmission in the brain, leading to increased seizure activity (Stewart, 2001). Melatonin is active in the cerebrospinal fluid (CSF), as it is in many other tissues (Agez et al., 2009).

Melatonin is produced in the absence of light, which limits movement during the night. Melatonin secretion in night-active organisms continues throughout the night. This leads to an increase in spontaneous movements. Melatonin plays an important role in establishing the circadian rhythm (Gunata et al., 2020).

Like many biochemicals in the body, plasma melatonin levels fluctuate over a 24-hour period. Pineal functions are acutely suppressed at night (Liebmann et al., 1997). Melatonin concentrations are much higher at night than during the day. Melatonin production usually starts at 21:00 and peaks at 04:00. Its level begins to decrease at approximately 07:00 in the morning. The secretion rate is 29 mg/day (Sack et al., 1998).

EFFECTS OF CIRCADIAN RHYTHM AND MELATONIN IN EXPERIMENTAL SEIZURE MODELS

Numerous studies have identified the anticonvulsant effects of melatonin in various seizure models. Melatonin (50 mg/kg) increased the maximum threshold of electroconvulsion in mice. Similarly, low-dose melatonin (25 mg/kg) increased the positive effects of carbamazepine and phenobarbital on electroshock-induced convulsions in mice (Borowicz et al., 1999). When administered at doses starting from 75 mg/kg, melatonin shortened the duration of generalized seizures by raising the post-discharge threshold in rats stimulated via the amygdala (Mevissen & Ebert, 1998). It also reduced PTZ-induced seizures in mice and guinea pigs (Yahyavi-Firouz-Abadi et al., 2007; Solmaz et al., 2009). Other experimental studies have also confirmed the anticonvulsant activity of melatonin against PTZ seizures (Mosińska et al., 2016; Tchekalarova et al., 2019; Hosseinzadeh et al., 2022). Melatonin (60 mg/kg) was effective against kainate-induced convulsions (Tchekalarova et al., 2022). Ramelteon, a melatonin receptor agonist, has been studied in two experimental studies. It reversed hippocampal excitability in a rat model. Ramelteon administered at 200 mg/kg reduced the seizure period and frequency in Kcna1-null mice. Improvements in the circadian rhythms of rest and activity were also detected (Fenoglio-Simeone et al., 2009). In a study examining intrahippocampal kainate administration in mice, ramelteon was reported to reduce oxidative stress, restore glutathione homeostasis, decrease microglia activation, and alleviate pro-inflammatory phenotypic changes in hippocampal astrocytes. In addition to these effects, ramelteon exerted a neuroprotective effect in the hippocampus, reducing memory impairment and depression-like behaviors (Park et al., 2024). Two studies of SE induced by electrical stimulation found more seizures during the day than at night (Quigg et al., 1998; Bertram & Cornett, 1994). The Kindling model has shown that seizure susceptibility in experimental epilepsy varies according to the time of day. Two studies on pilocarpine-induced SE found a significant increase in seizure rates during the day (Cavalheiro et al., 1991; Arida et al., 1999). A few in vitro reports have demonstrated the potential proconvulsive effects of endogenous melatonin. It has been reported that a concentration of 1 µmol melatonin increases epileptiform activity in hippocampal slices of rats. The proconvulsive effect is observed only during the daylight (Musshoff & Speckmann, 2003). Injecting melatonin receptor antagonists into the hippocampus in rats with pilocarpine-induced convulsions resulted in an increased latency to the dark phase, but this effect was not observed in the light phase. This effect may be due to endogenous melatonin's proconvulsive activity (Stewart & Leung, 2005).

Pilocarpine-induced status epilepticus causes chronic, spontaneously recurring seizures resembling temporal lobe epilepsy in humans. Experimental models have suggested that the frequency of behaviorally monitored seizures covaries with the circadian rhythm and increases over time. However, in a SE study conducted on 30-day-old rats, continuous video EEG recordings were obtained. Seizure frequency was not correlated with time of day in 11 chronic epileptic rats monitored on a fixed 12-hour light/dark cycle after SE. Although seizure distribution according to the circadian rhythm was not reported in this study, long-term observations showed regular or clustered patterns. This finding suggests that clusters with seizure-free intervals form in pilocarpine-induced spontaneous seizures. Therefore, short-term recordings may lead to errors in estimating seizure frequency. Accordingly, longer recording periods are needed to adequately assess an animal's seizure frequency (Bajorat et al., 2011). Unlike other studies, the lack of a significant difference in seizure frequency between light and dark periods is considered to be due to the chronic epilepsy model. In addition, ambiguities have arisen in studies using the universe model. One study found no difference in seizure occurrence between daytime and nighttime (Hellier & Dudek, 1999). Another study with similar total seizure frequency found that daytime seizures were more frequent (Raedt et al., 2009). These results do not eliminate the possibility that circadian influences indirectly determine seizure frequency, as more seizures occur during periods of inactivity/rest (Quigg et al., 1998; Hellier & Dudek, 1999; Quigg et al., 2000).

CIRCADIAN RHYTHM AND MELATONIN EFFECTS IN CLINICAL STUDIES

When melatonin was administered as an adjunctive treatment to six adult and pediatric patients with intractable seizures, five experienced a reduction in seizures, and two children showed decreased epileptic activity in their electroencephalogram (EEG) recordings (Peled et al., 2001). In one study, patients with generalized seizures were divided into two groups. The control

group received valproate and placebo, and the test group received valproate and melatonin. The melatonin-treated group had a lower seizure rate and improved quality of life (Verma et al., 2021). Sixty patients with idiopathic generalized seizures receiving valproate monotherapy were administered melatonin or placebo at 2-week intervals. Melatonin effectively reduced the mean severity score of epilepsy. Epileptic seizures did not decrease, but sleep quality improved (Maghbooli et al., 2023). Melatonin, administered as an adjunctive treatment, has shown beneficial effects against infantile epileptic spasm syndrome. Melatonin was added to adrenocorticotropic hormone and magnesium sulfate treatment at a dose of 3 mg per day. The patients' sleep quality improved. Although 85.7% of the patients slept regularly, this rate was 42.9% in the placebo group (Sun et al., 2024). Fewer studies have addressed melatonin's proconvulsive potential. One study administered melatonin (5 mg daily) to six neurologically impaired children with sleep disorders. Although sleep quality improved significantly, seizure activity increased in four children. This increase returned to baseline values after melatonin discontinuation (Sheldon, 1998). A 21-year-old woman who had several generalized tonic-clonic seizures was taking 600 mg carbapenem, 200 mg phenytoin, and 1,500 mg valproate daily. Proconvulsive effects were observed in the magnetoencephalography recordings after the administration of 1.5 mg melatonin. Furthermore, the patient experienced four brief seizures after taking melatonin (Sandyk et al., 1992).

The data regarding the effects of melatonin on seizures are conflicting. This indolamine may increase the seizure threshold and the protective effect of some antiseizure medications. Several studies have suggested that the effect of melatonin on seizures is attenuated (in vitro) with respect to both anticonvulsant and proconvulsant effects. Exogenous melatonin may have anticonvulsant effects, whereas endogenous indolamine may have proconvulsive effects (Kamieniak et al., 2024). Seizure activity may be associated with an increase in melatonin levels in the brain due to the circadian cycle (Stewart, 2001).

EFFECTS OF CIRCADIAN RHYTHM AND MELATONIN ON EPILEPTIC DISCHARGE

Under normal conditions, the electrical activity of the brain is not synchronized. Synchronized neuronal discharges represent the neurobiology basis of epilepsy. These synchronized discharges are usually associated with a group of neurons in the cortex and form epileptic foci. Over time, they can spread to different parts of the brain, causing epilepsy, including abnormal behaviors and thoughts (Conde-Blanco et al., 2021). Convulsive seizures may occur because neurons are stimulated at a higher frequency than normal. Furthermore, epilepsy is associated with a low neuronal excitability threshold (Khan et al., 2018).

Antiseizure medications exert their effects through inhibitory actions on voltage-modulated ionic channels (mainly sodium channels), enhancement of inhibitory transmission (GABAergic), and suppression of excitatory transmission (especially glutamatergic transmission) (Khan et al., 2018). In the first of these effects, voltage-dependent sodium channels open during stimulation, causing rapid depolarization, which in turn triggers neurotransmitter release at the axon terminal and then close rapidly. New stimulation may be possible by reopening these channels. Some antiseizure medications prolong the inactivated of these channels (Kaplan, 2016; Catterall, 2014). Excessive stimulation is blocked by gamma-aminobutyric acid neurons (Treiman, 2001). Antiseizure drugs prevent the excessive activation of N-methyl-D-aspartate receptors by glutamate and glycine (Zhou & Sheng, 2013).

Studies have shown that a significant portion of melatonin is localized in the cell nucleus. Melatonin has specific binding sites in the cell nucleus (Penev & Zee 1997). Quantitative in vitro studies have shown that melatonin receptors are present in the brain and peripheral tissues (Gunata et al., 2020). Furthermore, it may reduce epilepsy by closing voltage-dependent Ca channels and suppressing neuronal activity (Choi et al., 2014).

CIRCADIAN RHYTHM AND MELATONIN'S EFFECT ON SLEEP

Although epileptic activity is sometimes considered sudden, it recurs regularly at similar times each day or during a particular wakefulness state. This review focuses on the role of the 24-hour circadian rhythm in the occurrence of seizures and the sleep-wake cycle associated with seizures. Circadian rhythmicity is a key factor in adaptation to approximately 24-h environmental cycles. Several physiological processes and similar pathological events occur within a specific circadian range. Brain activity, neuronal excitability, and stress hormones that trigger seizures follow a circadian pattern. This also applies to epilepsy in general (Smyk & van Luijtelaar 2020). Seizures were initially classified as diurnal, nocturnal, or diffuse, with no specific time of day characteristics (Gowers 1885; Langdon-Down & Brain 1929). More recent studies have linked the temporal pattern of seizures to the epileptic focus location. For example, seizures originating from the temporal lobe are most common during the day, whereas those originating from the frontal and parietal lobes are more common at night (Quigg et al., 1998; Quigg & Straume, 2000; Pavlova et al., 2004; Durazzo et al., 2008; Hofstra et al., 2009a; Karafin et al., 2010; Zarowski et al., 2011; Loddenkemper et al., 2011; Kaleyias et al., 2011; Nzwalo et al., 2016). The typical 24-hour rest/activity cycle in humans and the day/night preference for seizures may reflect a predisposition to a particular alertness state. Indeed,

different levels of brain excitability and sleep-wakefulness are important factors affecting the seizure threshold (Steriade & Contreras 1995). Temporal and occipital lobe seizures were more common during wakefulness and frontal lobe seizures during sleep in patients with focal epilepsy (Pavlova et al., 2004; Hofstra et al., 2009a; Kaleyias et al., 2011; Crespel et al., 1998; Herman et al. 2001; Hofstra et al. 2009b; Yildiz et al., 2012). Interestingly, this pattern varies with age. Frontal lobe seizures are more common in infants when they are awake, whereas they are more common during sleep in adolescents (Ramgopal et al. 2014). Generalized seizures occur more frequently during wakefulness (Zarowski et al. 2011; Loddenkemper et al., 2011; Winawer et al., 2016). The cyclical repetition of when people are asleep and awake is a circadian rhythm. The temporal organization of sleep also depends on homeostatic mechanisms. Retrospective analyses of EEG, video EEG, or intracranial recordings taken over several days for diagnostic or epileptic surgery have reported inhomogeneous seizure distribution and a relationship between seizures and sleep and wakefulness. With new technological developments, long-term monitoring of epileptic activity outside the clinic, up to several years, has now become possible. Such studies have confirmed the existence of stable 24-hour rhythms but also longer rhythms in epileptic seizures. These rhythms vary depending on the epileptic focal point location and patient characteristics (Spencer et al., 2016; Karoly et al., 2016, 2017, 2018; Baud et al., 2018; Weisdorf et al., 2019). Recent studies in humans and rat models have revealed that seizures recur consistently in epileptic events, depending on the phase of circadian and multidynamo rhythms, suggesting endogenous mechanisms of such periodic rhythms, their co-regulation, and the interrelationship between seizures and IEDs (Karoly et al., 2017; Baud et al., 2019).

Internal and external synchronization are important for human health. For example, disruption of circadian rhythms due to shift work can lead to health problems and increased risks of cancer, metabolic, neurodegenerative, cardiovascular, or mental illnesses (Hedström et al., 2011; Kecklund & Axelsson 2016; Wyse et al. 2017; Stenvers et al., 2019). Deviations from the established rhythm, such as inconsistency between sleep and wakefulness, are signs of serious pathological changes in the body (Musiek et al., 2018; Smagula et al., 2019). Cardiovascular diseases, such as stroke, myocardial infarction, arrhythmia, and sudden cardiac death, are more likely to occur in the early hours of the day (Karmarkar & Tischkau 2013; Buurma et al., 2019). Nervous system-related symptoms are also associated with circadian modulation. Mood deterioration generally occurs in the morning in patients with migraine and major depressive disorder (Murray 2008; Morris et al., 2009; Baksa et al., 2019). In some patients with AD, behavioral symptoms deteriorate during sunset, afternoon, and evening hours. This is related to the rhythm of body temperature (Volicer et al., 2001; Bachman & Rabins 2006; de Jonghe et al., 2010). Epilepsy is a brain disease with epileptic seizures and circadian phenotypic expression. Numerous studies have demonstrated that epilepsy is closely related to sleep. Treating sleep disorders also positively impacts epilepsy. Preclinical studies have demonstrated that melatonergic compounds, such as agomelatine, have a positive effect on seizures and anticonvulsant effects. However, these findings need to be tested in clinical studies (Tchekalarova et al., 2015). Melatonin showed a potent anticonvulsant effect when administered with sodium valproate in an experimental rat study (Savina et al., 2006). Human studies and a significant number of experimental animal studies suggest that melatonin is an effective antiepileptic agent. Indoleamine may be effective against circadian rhythm-independent seizures (Kamieniak et al., 2024). Melatonin can be administered as an adjuvant in patients with epilepsy and comorbid sleep disorders (Vimala et al., 2014; Jiang et al., 2024; Singh et al., 2025).

EFFECTS OF CIRCADIAN RHYTHM AND MELATONIN ON COGNITIVE ACTIVITY AND MEMORY LEARNING IN EPILEPSY

Melatonin treatment during epileptogenesis increased seizure latency in a kainate-induced temporal lobe epilepsy model (10 mg/kg diluted in drinking water for 8 weeks) It reduces the frequency of spontaneous uncontrollable seizures and attenuates seizure activity. It does not affect disrupted circadian rhythms and behavioral disorders due to epilepsy (Petkova et al., 2014). In a study in which melatonin (10 mg/kg), administered 3 days after kainate injection and for 1 week, decreased the frequency of spontaneous seizure activity recorded by EEG compared with a single dose. Repeat indolamine injections reduced the number and severity of spontaneous behavioral convulsions. In addition, mice pretreated with melatonin showed improvements in cognition, learning, and memory tasks, and a neuroprotective effect was also detected in the hippocampus (Li et al., 2023).

Chronic intraperitoneal melatonin administration increases neuronal GluR2 surface expression in the CA1 region, which may reduce Ca2+ permeability, alleviate epilepsy-induced LTP deficits, and save neurons from death. This may also alleviate cognitive dysfunction in rats with chronic-phase epilepsy (Ma et al., 2017). This study highlights the role of melatonin in the prevention of epilepsy-related cognitive impairments.

A study investigating the quality of life of 31 children treated with valproate alone, 16 of whom received additional melatonin, reported significant improvements in memory and language subscales, cognitive function, and anxiety-like behaviors in the

melatonin group (Gupta et al. 2004a). The paucity of human studies, coupled with the small number of controlled clinical studies, leaves some topics unanswered (Sanchez-Barcelo et al., 2010). According to current scientific data, melatonin can change the electrical activity of neurons. However, its effect on the CNS has not yet been fully elucidated (Leon et al., 2000). Studies on this topic indicate that melatonin improves the condition of patients with epilepsy. A study has shown that melatonin application has a positive effect on children with epilepsy. Melatonin was associated with physical function, emotional recovery, and behavioral improvements (Gupta et al. 2004b).

EFFECTS OF CIRCADIAN RHYTHM ON BIOLOGICAL DATA IN EXPERIMENTAL EPILEPSY MODELS

The effects of circadian clock genes on the pathophysiology of epilepsy and behavioral disorders caused by epilepsy need to be investigated. A study involving female rats characterized the nighttime expression of these genes. This study demonstrated that circadian dysfunction is a fundamental consequence of epilepsy and emphasized that future studies and a comprehensive assessment of circadian disruption will shed light on the feasibility of chronotherapy interventions in patients with epilepsy (Yamakawa et al., 2023).

The circadian clock also modulates aging-associated systems, such as the oxidative stress response and DNA repair (Kondratova & Kondratov 2012). Disrupted circadian rhythms affect melatonin production, which negatively impacts the health of older individuals (Poeggeler, 2005). Aging causes changes in the daily expression of various clock genes in the SCN. Melatonin is effective in correcting age-related changes. Clock gene mRNA expression at 3, 12, and 24 months demonstrates that age-dependent circadian changes In an experimental study, 11 days of melatonin administration restored Per2, Cry1, Cry2, and Bmal1 to normal rhythms (Jenwitheesuk et al., 2014). This literature suggests a causal link between clock genes and molecular factors that cause nerve damage.

PRACTICAL RESULTS, CHALLENGES, CHRONOTROPY-BASED EPILEPSY TREATMENTS, AND FUTURE OUTLOOK

Melatonin may exert this effect because of its biological and chemical properties. Melatonin exerts antioxidant, free radical scavenging, immune regulation, and anti-inflammatory effects and regulates the circadian rhythm (Sahna et al., 2005).

According to the literature, melatonin has both positive and negative effects on epilepsy (Gunata et al., 2020).

This review focuses on melatonin's lipophilic and hydrophilic properties, its ability to easily cross the blood-brain barrier, and its effects on the neurological system. According to one study, 50–100 mg of melatonin per day is sufficient for the treatment of neurological diseases (Cardinali et al. 1998). One of the most important issues in studies investigating the effectiveness of melatonin, a neuroprotective agent, is accurately determining the optimal dose. Using significantly higher doses in experimental animals than in clinical studies affects the results. Further research is needed to increase the therapeutic efficacy of existing treatment methods, reduce their side effects and toxicity, and investigate the protective and therapeutic effects of melatonin in neurological diseases (Gunata et al., 2020). The temporal organization of epileptic seizures and their predominance during wakefulness offer promising practical implications for diagnosis, treatment, and new approaches. Sleep deprivation and sleep fragmentation are currently recognized as triggering factors in some seizure types (Rosenow et al., 2015). The variation in seizure timing across the sleep-wake cycle is considered a promising criterion for determining the epileptic zone in intractable epilepsies (Klimeš et al. 2019).

Pharmacology can also be used to study the rhythmic distribution of epileptic reflexes. Timed drug administration, a branch of chronopharmacology, is already used for treating cardiovascular diseases (Smolensky & Peppas 2007). Studies have investigated the effects of the circadian cycle on the pharmacokinetics and anticonvulsant effects of antiepileptic drugs in patients with epilepsy (Hofstra et al., 2012; Ramgopal 2013). Studies with fully validated data, carefully selected patient populations, and well-designed preclinical models can reveal the relationship between circadian rhythm and epilepsy. Obtaining homogeneous patient groups for investigating circadian rhythms in epilepsy is challenging, and most studies are retrospective. Furthermore, it is challenging to make a clear distinction regarding observed rhythmicity, whether in standard clinical settings or in home settings. Therefore, the circadian timing system influences both sleep need and duration. Observational studies that consider seizure timing may not fully explain whether the endogenous clock or the sleep-wake cycle drives the epileptic activity cycle (Smyk & van Luijtelaar 2020).

Patients with epilepsy commonly experience cognitive, learning, memory, anxiety-like behavioral problems, and general behavioral problems due to seizures and neurodegeneration. Various treatment trials and research are being conducted to treat patients with epilepsy and, if possible, completely cure or at least alleviate such problems. However, the data obtained from these studies sometimes report contradictory results. It is impossible for the seizure parameters and cognitive and behavioral characteristics tested in these studies to be unaffected by the circadian rhythm. This has been demonstrated in numerous studies.

CONCLUSION

In clinical studies, it is essential to pay attention to characteristics such as age, race, gender, and lifestyle that may affect the biological parameters of the patients under study. All criteria, including the cause of epilepsy, its focus, mechanism, and study duration, should be considered. Otherwise, the interpretation of the obtained data may lead to erroneous interpretations. This is because daily light exposure, sleep quality and duration, and other stress factors or advantages will influence the results of these studies.

Criteria such as age, species, breed, gender, and housing conditions of the animals used in experimental studies will also influence the research results. Animal diet, exposure to light, additional stress, or the opposite will also affect the results. It is important to remember that rodents, which are particularly active at night, rest during the day. Sleep deprivation and the conduct of tests and procedures that cannot be completed simultaneously, especially behavioral tests, in different sessions can make it difficult to implement the rule of performing the same procedure in the same timeframe. However, the effects of these negative situations can be minimized with good planning by performing the same procedures for all groups in the same timeframe. Otherwise, the reliability of the obtained data will be reduced.

The mechanisms of action of the drugs used in treatment trials should also be carefully examined and considered in the evaluation of the tests. For example, benzodiazepine-induced stimulation of the GABAergic system reduces melatonin levels at night (Monteleone et al., 1997). Furthermore, melatonin levels should be monitored after drug administration because dopaminergic agonists or opioid receptor blockers can alter melatonin release (Gunata et al., 2020).

In conclusion, for the accuracy and interpretation of data used in intergroup comparisons, circadian rhythm and, consequently, the variable serum melatonin concentration must be considered in clinical or experimental studies on epilepsy treatment. The parameters studied cannot be unaffected by the circadian rhythm and melatonin concentration.

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