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Review

Melatonin in experimental seizures and epilepsy

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Abstract:
Although melatonin is approved only for the treatment of jet-lag syndrome and some types of insomnia, clinical data suggest that it is effective in the adjunctive therapy of osteoporosis, cataract, sepsis, neurodegenerative diseases, hypertension, and even cancer. Melatonin also modulates the electrical activity of neurons by reducing glutamatergic and enhancing GABA-ergic neurotransmission. The indoleamine may also be metabolized to kynurenic acid, an endogenous anticonvulsant. Finally, the hormone and its metabolites act as free radical scavengers and antioxidants. The vast majority of experimental data indicates anticonvulsant properties of the hormone. Melatonin inhibited audiogenic and electrical seizures, as well as reduced convulsions induced by pentetrazole, pilocarpine, L-cysteine and kainate. Only a few studies have shown direct or indirect proconvulsant effects of melatonin. For instance, melatonin enhanced low Mg^{2+}-induced epileptiform activity in the hippocampus, whereas melatonin antagonists delayed the onset of pilocarpine-induced seizures. However, the relatively high doses of melatonin required to inhibit experimental seizures can induce some undesired effects (e.g., cognitive and motor impairment and decreased body temperature).
In humans, melatonin may attenuate seizures, and it is most effective in the treatment of juvenile intractable epilepsy. Its additional benefits include improved physical, emotional, cognitive, and social functions. On the other hand, melatonin has been shown to induce electroencephalographic abnormalities in patients with temporal lobe epilepsy and increase seizure activity in neurologically disabled children. The hormone showed very low toxicity in clinical practice. The reported adverse effects (nightmares, hypotension, and sleep disorders) were rare and mild. However, more placebo-controlled, double-blind randomized clinical trials are needed to establish the usefulness of melatonin in the adjunctive treatment of epilepsy.

Key words:
melatonin, epilepsy, seizures, pineal gland

Abbreviations: ADHD – Attention Deficit Hyperactivity Disorder, ADT – afterdischarge threshold, CNS – central nervous system, CST – clonic seizure threshold, FDA – Food and Drug Administration, GABA – γ-aminobutyric acid, *icv* – intracerebroventricular, *ip* – intraperitoneal, *iv* – intravenous, *po* – per os, PTZ – pentylenetetrazole, QOL – quality of life, QUIN – quinolinic acid, *sc* – subcutaneous

Introduction

Melatonin (N-acetyl-5-methoxytryptamine; Fig. 1), an indoleamine derivative of serotonin, was first isolated in the late 1950s by Aron Lerner and coworkers [14, 45]. The hormone is produced in the pineal gland, a part of the epithalamus, and remains one of the most mysterious substances produced by the human body. How melatonin works and its exact role in humans are not yet fully understood. Multidirectional research has been conducted to determine all of the medical implications of the administration of exogenous melatonin.

The pineal gland is the major, but not the only, source of melatonin in humans [26], which is also synthesized in multiple cells and organs, including the

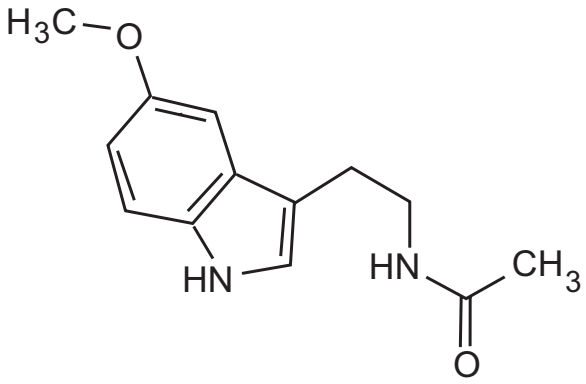

Fig. 1. Structure of melatonin (N-acetyl-5-methoxytryptamine)

retina, gastrointestinal tract, and bone marrow. Furthermore, the hormone is measurable in the cerebrospinal fluid and blood [13, 63, 83, 84]. Because no pineal storage of melatonin seems available, plasma hormone concentrations reflect the pineal activity [30]. Melatonin production is heavily dependent on circadian rhythms generated by the light/dark cycle. The endogenous rhythm is characterized by a low daytime level, ascending after the onset of darkness to high output during the night (with a peak between 3 and 4 a.m.), and then falling sharply before sunrise [16, 30, 97]. Therefore, it is often described as the "hormone of darkness" or "dark force". The biological rhythm of secretion is generated by the suprachiasmatic nuclei. The photic information is transmitted from the retina to the pineal gland *via* the hypothalamus and superior cervical ganglion to control the timing of melatonin synthesis [48]. Finally, norepinephrine released during darkness acts on adrenergic receptors to promote the nocturnal synthesis of melatonin [70].

The melatonin concentration in blood may vary among individuals depending on their sex, age and co-morbid diseases. The peak of the hormone secretion corresponds closely to the nadir of body temperature [6]. In humans, melatonin is first measurable in babies of 3–6 months. Its production reaches the maximal level at 1–5 years and starts to decrease around the beginning of puberty. It is interesting that elderly women show higher levels of melatonin than do elderly men [14, 40, 82].

The melatonin half-life in serum varies between less than 30 minutes and 60 minutes. It is metabolized primarily in the liver, and secondarily in the kidney [11, 35]. Circulating melatonin is primarily hydroxylated by the microsomal cytochrome P_{450} monooxygenases (isoenzymes CYP1A2, CYP1A1 or CYP1B1) to 6-hydroxymelatonin, and then excreted in urine as sulfate and, to a lesser extent, glucuronide conjugates. Only about 1% of melatonin remains unchanged [15]. It is interesting that the cerebral pool of melatonin may be metabolized to kynurenic acid, a natural substance with anticonvulsant properties [57].

According to Reiter et al. [70], melatonin is not, in the strictest sense, a hormone because it does not fulfill the criteria of the conventional definition. It is rather a tissue factor, an antioxidant, an autacoid, or a paracoid depending on where and how it acts [83]. Although melatonin is produced in many different tissues and organs, its main action refers to the central nervous system (CNS). This indoleamine derivative has multiple receptor-mediated and receptor-independent actions. Its binding sites and receptor messenger RNA have been detected in the hypothalamus, pituitary, retina, thalamus, hippocampus, and neocortex in a variety of mammalian species, including humans [25, 48]. Melatonin acts *via* two receptors, designated as the MT1 (alternative nomenclature: Mel1a, ML1a) and MT2 (Mel1b, ML1b) subtypes. The effector systems involved in MT1 and MT2 receptor signaling through high-affinity G-protein coupling include adenyl cyclase, phospholipase C, phospholipase A2, potassium channels, and possibly guanylyl cyclase and calcium channels. Activation of these receptors causes dissociation of G-proteins into α and $\beta\gamma$ dimers, which then interact with various effector molecules. MT1 receptors are more prevalent than MT2 receptors in the hippocampus [25, 55, 58, 70]. Third, a low-affinity membrane receptor named MT3 is less known. It modulates calcium and calmodulin activity, thereby evoking a decrease of intraocular pressure [61, 65].

Undoubtedly, melatonin plays a role in many behavioral processes. At physiological concentrations, it regulates the endogenous clock function [5, 41]. In fact, the sleep/wake cycle is synchronized with the 24-h blood melatonin cycle [23]. Administration of melatonin at pharmacological doses improved sleep initiation and continuity throughout the night in children with sleep disorders. Studies that included blind children and children with neurodevelopmental disabilities have reported significant improvements in sleep patterns [24, 32]. Melatonin may be a new well-tolerated treatment option for children with Asperger disorders suffering from chronic insomnia [62]. It also

enhanced the total time asleep in children with Attention Deficit Hyperactivity Disorder (ADHD) [86].

Exogenous melatonin is able to influence endogenous secretion of the hormone according to a phase response curve. There are some therapeutic implications for this property in situations when biological rhythms are disturbed (jet-lag syndrome, delayed sleep phase syndrome, insomnia in the blind or elderly people, shift-work) [16].

Melatonin is also a potent scavenger of both Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS). It also stimulates the activity of antioxidative enzymes that convert ROS to innocuous molecules [68]. Moreover, melatonin decreases electron leakage from mitochondria, thereby diminishing free radical generation [39]. All of these processes reduce lipid and protein peroxidation, as well as DNA damage. For instance, melatonin (1.5 mM) completely abolished lipid peroxidation and mitochondrial damage triggered by kainic acid in mice brain homogenates [53, 94, 95]. Additionally, melatonin may also exert a neurobiologically relevant action by interacting with nuclear receptors [12, 53, 66, 95]. It should be noted that other antioxidants, like ascorbate or tocopherol, may function under certain circumstances as pro-oxidants. In contrast, melatonin has not been shown to present such properties [68]. The fact that melatonin easily passes the blood-brain barrier makes it of major importance in protecting the brain and reducing neuron excitability [71]. However, it was also reported to attenuate free radical damage in the course of cataract, hyperthyroidism, sepsis, and septic shock [69]. In animals, melatonin prevented caerulein-induced pancreatitis (AP) in rats through the activation of the antioxidative defense mechanisms in pancreatic tissue [37]. There is evidence that melatonin secretion significantly declines during menopause. Several reports indicate that this hormone is involved in the regulation of bone metabolism and increases total bone density. Therefore, it may be beneficial in reducing the severity of postmenopausal osteoporosis [72, 81]. In animals, melatonin influences the endocrine reproductive axis [22]. In humans, these relationships are less clear. The rhythms of melatonin and reproductive hormones are closely related in infancy and reciprocally correlated during puberty. Melatonin receptors have been demonstrated in reproductive organs, whereas sexual hormone receptors have been discovered in the pineal gland. However, it is not known whether these two are functionally related [47].

According to data in the literature, melatonin shows some *in vitro* antiproliferative effects realized through the MT1 and MT2 receptors. Beneficial action has been observed in various cancer types (breast, lung, metastatic renal cell carcinoma, hepatocellular carcinoma, brain metastases from solid tumors, ovarian carcinoma, human neuroblastoma cells, bladder carcinoma, and erythroleukemia) [14, 67].

Melatonin affects the immune response. Its immunomodulatory effects were observed in patients with bronchial asthma. The nocturnal rise in blood melatonin levels was associated with an increased production of interleukins (IL-1, IL-2, IL-6, IL-12), thymosin 1a, thymulin, and TNFα [51]. The hormone acts on immunocompetent cells (monocytes, B-lymphocytes, natural killer lymphocytes, T-helper lymphocytes, cytotoxic T-lymphocytes), and enhances cytokine production/secretion, cell proliferation and oncostasis [46]. On the other hand, the immune system regulates pineal gland functions *via* cytokines produced by activated immune cells [77].

Manev et al. [49] reported that resection of the pineal gland enhanced neurodegeneration evoked in two models of focal brain ischemia/stroke and in glutamate receptor-mediated experimental seizure. This may suggest that endogenous melatonin acts as a neuroprotective factor, and its deficiency might be involved in the pathogenesis of neurodegenerative diseases [49].

Although accumulating evidence suggests that melatonin modulates the electrical activity of neurons, its role in the CNS is still poorly understood. Melatonin (at concentrations corresponding to its nocturnal peak) may inhibit calcium influx into the neurons and bind to the calcium-calmodulin complex, thus inhibiting neuronal nitric oxide synthase (nNOS) activity, diminishing NO production, and therefore reducing the excitatory effect of N-methyl-D-aspartate [44, 57]. According to Acuña-Castroviejo [2], melatonin specifically inhibits the NMDA subtype of excitatory glutamatergic receptors in rat striatum. Moreover, the indoleamine increases brain GABA concentrations and receptor affinity [4, 60], and potentiates brain inhibitory transmission *via* GABA-ergic synapses [80, 88]. Several data suggest the involvement of calcium ions in the effects of indoles, and it seems that melatonin acts as an antagonist of L-type calcium channels [1]. The physiological effects of melatonin may also involve a reduction of striatal dopaminergic

Tab. 1. Effects of melatonin in animal models of epilepsy

The effects of melatonin in animal models of epilepsy		
Model of seizures	Dose and type of treatment	Mode of action [ref.]
seizures induced by maximal electroshock in mice	25 mg/kg, *ip*	anticonvulsant [10]
penicillin-induced epileptiform activity in rats	40 and 80 μg, *icv*	anticonvulsant [96]
seizure induced by pilocarpine in rats	10–50 mg/kg, *ip*	anticonvulsant [17]
seizure induced by PTZ (*iv*) (NO pathway) in mice	40–80 mg/kg, *ip*	anticonvulsant [91]
seizure induced by PTZ (*icv*) in mice	10.0 μg, *icv*	anticonvulsant [42]
seizure induced by PTZ (*ip*) in mice	10.0 μg, *icv*	ineffective [42]
induced by PTZ (*iv*) clonic seizure (with morphine)	40, 80 mg/kg, *ip* and 10 mg/kg, *ip*	anticonvulsant and proconvulsant – depending on doses of melatonin [92]
seizure induced by PTZ (*ip*) in guinea pigs	10 mg/kg, *ip*	anticonvulsant [78]
seizures induced by kainite and QUIN	5.0–10.0 μg, *icv* and 12.5–100.0 mg/kg, *ip*	anticonvulsant [42]
amygdala kindling in rats	≥75 mg/kg, *ip*	anticonvulsant [52]
pineal gland removal on kindling model	–	anticonvulsant [20, 36]
pinealectomy in the pilocarpine model of epilepsy in rats	–	anticonvulsant [21]
inhibition of a specific subtype of melatonin receptor	–	proconvulsant [80]

activity *via* the dopamine D_1 and D_2 receptors, which in turn inhibit glutamate release [79, 82]. Finally, melatonin may be metabolized not only to kynurenic acid, as mentioned above [57], but also to N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK), and N^1-acetyl-5-methoxykynuramine (AMK). These metabolites are very powerful antioxidants and cyclooxygenase-2 inhibitors. Therefore, they are considered as potential selective anti-inflammatory agents [39, 51]. All of these mechanisms are suggested to be associated with the sedative, hypnotic, anxiolytic, anticonvulsive, and analgesic effects of melatonin [19, 31]. In light of the cited data, it seems interesting that $GABA_A$ and benzodiazepine receptor activity in the cerebral cortex of rats exhibits a circadian rhythm that depends on the existence of an intact pineal gland [3].

Clinical data have indicated that the peak of the circadian seizure profile falls for the nocturnal period [66]. This refers to more than 60% of seizures [50]. Although the exact mechanism responsible for seizure periodicity remains unknown, a diurnal rhythm in convulsive sensitivity would relate to a time-dependent biological signal that is generated by intrinsic neural oscillators. Interestingly, a normal circadian pattern of melatonin secretion is observed in active epilepsy, with the exception that nocturnal secretion is two-fold higher in untreated epileptic patients than in healthy control subjects. Elevated and reduced melatonin levels at various stages of the reproductive cycle may account for the fact that epileptic women experience an increase in seizure activity during menstruation and pregnancy, as well as a significant reduction in seizure episodes during menopause [66]. Our knowledge of melatonin function in epilepsy has greatly increased in recent years, but still remains controversial. Questions regarding the anticonvulsive activity of melatonin have not yet been fully answered.

Currently, melatonin and ramelteon (an agonist for melatonin receptors) are approved by the US Food and Drug Administration (FDA) only for the treatment of insomnia characterized by difficulty with sleep onset. Despite the fact, it has been released for public use by the FDA and is available over the counter nationwide, information on the toxicology of melatonin seems to be insufficient. Attention should be paid to the possible side effects of

melatonin, such as nightmares, hypotension, sleep disorders, and abdominal pain. Ramelteon may induce headache, dizziness, somnolence, and nausea. However, the vast majority of studies document the very low toxicity of melatonin and its derivatives over a wide range of doses [9, 33].

Melatonin in animal models of epilepsy

Anticonvulsant properties

Animal models of epilepsy play a fundamental role in our understanding of the basic physiological and behavioral changes associated with human epilepsy and its relationship with melatonin. Much of the available literature suggests anticonvulsant effect of melatonin. Only few works report a proconvulsant role of this hormone in experimental epilepsy (Tab. 1).

The results obtained from *in vitro* experiments did not show any anticonvulsant properties of melatonin. However, the majority of data were received from experiments conducted *in vivo*. Mevissen et al. [52] reported that melatonin, applied at doses 75 mg/kg or higher, significantly increased the afterdischarge threshold, and suppressed generalized seizures in amygdala kindled rats, the established model for temporal lobe human epilepsy. According to the authors, seizure susceptibility seems to not depend on the circadian variation of endogenous melatonin, because the highest thresholds were found in the morning, when endogenous melatonin levels are low [52]. It is likely that changes in the levels of other endogenous substances, like glucocorticoids, might be responsible for the increase of seizure susceptibility at night [89]. The lack of any protective effects of endogenous melatonin may suggest that its physiological concentrations are too low to affect seizure susceptibility in the brain. Janjoppi and colleagues [36] examined the influence of pineal gland removal on the kindling model. The pinealectomy exerted a significant influence on amygdala kindling development by reducing the number of stimulations needed to reach stage 5. This suggests that endogenous melatonin may act as a neuroprotective factor [36]. Another study revealed that a physical exercise program reversed acceleration of the kindling process in pinealectomized animals [20]. However, the mechanisms of this phenomenon remain unknown.

Experiments conducted in mice showed that melatonin (50 mg/kg) significantly raised the electroconvulsive threshold, and when administered at a subprotective dose of 25 mg/kg, it enhanced the anti-electroshock activity of carbamazepine and phenobarbital. This effect was reversed by bicuculline, aminophylline, and picrotoxin used at subconvulsive doses, which may suggest that the anti-electroshock efficacy of melatonin depends on purinergic and GABA-ergic neurotransmission. Unfortunately, melatonin administered alone or in combination with antiepileptics significantly impaired long-term memory in mice [10].

Costa-Lotufo and co-workers [17] demonstrated that subchronic (10–50 mg/kg, *ip* for a week at 8.30 h or 17.00 h) but not acute treatment with melatonin increased the latency of pilocarpine-induced convulsions in rats. The authors suggested that this effect seemed to be more intense at the light-dark transition. However, the differences were not significant; thus, in our opinion, this conclusion was rather premature. Moreover, melatonin increased the number of [^{3}H]GABA binding sites in animal hippocampal slices. This in turn may suggest that the revealed action of melatonin may be due to positive modulation of GABA-ergic transmission [17].

Pinealectomy in the pilocarpine model of epilepsy in rats reduced the latency for the first spontaneous seizures and increased the number of spontaneous seizures during the chronic period. However, supplementation of melatonin during the status epilepticus (acute) period was able to reduce the number of TUNEL-positive (apoptotic) cells in several limbic areas. This may suggest that epileptogenic facilitation induced by pilocarpine can be partially reverted by the simultaneous administration of melatonin [21].

Yildirim and Marangoz [96] observed anticonvulsant effects of melatonin on penicillin-induced epileptiform activity in rats. Melatonin administered intracerebroventricularly (*icv*) (40 and 80 μg) prolonged the latency of epileptiform activity as analyzed by electrocorticogram. Furthermore, melatonin significantly decreased the spike frequency and spike-wave activity, whereas the amplitude of spikes remained unchanged [96]. The proconvulsant action of penicillin used to be explained by its non-competitive antagonism towards $GABA_A$ receptors [18]. Positive modulation of GABA receptors and increased GABA concentrations induced by melatonin can explain its anticonvulsant activity in this model of epilepsy [4].

In the study of Yahyavi-Firouz-Abadi et al. [92], it was revealed that acutely administered melatonin (40 and 80 mg/kg) significantly elevated the clonic threshold of convulsions induced by intravenous (*iv*) injection of pentetrazole (PTZ) in mice. Moreover, a combination of melatonin, applied at subprotective doses (10 and 20 mg/kg), with L-arginine also resulted in a potent anticonvulsant action. On the other hand, pretreatment with non-specific NOS inhibitors attenuated the effect of melatonin. These findings may imply involvement of the L-arginine/NO pathway in the melatonin-induced modulation of seizure susceptibility in mice [91]. In fact, melatonin (applied at 10–40 mg/kg) counteracted PTZ-induced glutamine and aspartate increases, whereas at higher doses (40–160 mg/kg), it decreased nitrite content in several brain areas, including the hippocampus [8]. Pretreatment (*icv*) with melatonin (1.25–10 μg) reduced (in descending order of potency) the convulsant action of *icv* administered kainate, quinolinate, glutamate, N-methyl-D-aspartate, and PTZ. Intraperitoneal (*ip*) injections of melatonin (12.5–100.0 mg/kg) attenuated the convulsant activity of quinolinate but not the remaining substances. A possible explanation is that the brain concentrations of melatonin after systemic injection are too low to reach significant anticonvulsant levels [43]. According to Yamamoto and co-workers, melatonin at a dose of 20 mg/kg, *sc* prevented L-cysteine-induced seizures and brain lipids peroxidation in mice. The authors concluded that the anticonvulsant effect of melatonin may be, at least partially, due to its antioxidative action [95].

Uz et al. [85] tested the *in vivo* efficacy of melatonin in preventing kainate-induced DNA damage in the hippocampus of adult rats. They suggested that melatonin might reduce the extent of cell damage mediated through kainate receptors [85].

Other authors have observed that the simultaneous *ip* administration of melatonin (20 mg/kg) and kainic acid completely abolishes kainate-induced seizures in mice and mitochondrial DNA damage in the mouse brain cortex [53, 95]. The scavenging of hydroxyl radicals may contribute to both the anticonvulsant and protective effects of melatonin [53]. On the other hand, a number of substances with antioxidant properties, like vitamin E, vitamin C, α-lipoic acid, and melatonin (20 mg/kg, *ip*), failed to affect kainate- or PTZ (*sc*)-induced convulsions in rats [90]. This may suggest that antioxidative properties are not efficient in terms of seizure inhibition.

Solmaz et al. [78] reported that melatonin (10 mg/kg) pretreatment before PTZ (*ip*) administration lowered the mortality rate, attenuated seizure severity, and increased seizure latency in guinea pigs.

In another study, melatonin (10 mg/kg) potentiated both the anticonvulsant and proconvulsant effects of morphine, applied at low and high doses, respectively, on the PTZ-induced clonic seizures in mice [92]. In addition, this effect was reversed by L-NAME (a nitric oxide synthase inhibitor). This may indicate that melatonin modulates opioid neurotransmission *via* the nitric oxidergic pathway. Because there is also evidence that opioid peptides regulate pineal function [87], this relation may be bidirectional. Moreover, it should be noted that the anticonvulsant effect of both melatonin [80] and morphine [42, 56] was associated with increased central GABA-ergic transmission. It cannot be excluded that melatonin indirectly stimulates GABA transmission *via* the opioid system activation.

Savina et al. [74] reported that combined treatment with sodium valproate (*po*) and melatonin (*po*, 50 mg/l) produced a potent anticonvulsant effect, i.e., increased the latency and decreased the severity of audiogenic seizures in Krushinskii-Molodkina rats.

Additionally, the *icv* injection of antimelatonin antibody in rats induced paroxysmal neural discharges, suggesting that melatonin may normally act as an endogenous inhibitor of neural excitability [27].

Proconvulsant properties

Only a few studies have shown proconvulsant effects of melatonin. Stewart and Leung [80] provided evidence that endogenous melatonin may decrease the seizure threshold in rats. Intrahippocampal injection of 4-phenyl-2-propionamidotetralin, a specific Mel1b melatonin receptor antagonist, delayed the onset of pilocarpine seizures during the dark phase, but not the light phase. This effect was blocked by co-administration of the $GABA_A$ antagonist bicuculline. The mixed Mel1a/Mel1b receptor antagonist luzindole also increased seizure latency but to a lesser degree than 4-phenyl-2-propionamidotetralin. This may suggest that the Mel1b receptors attenuate $GABA_A$ receptor-mediated inhibition [80].

In another study, melatonin, when administered in a near-physiological concentration of 10 nM/l, exerted no effect on epileptiform potentials elicited in hippocampal slices by low Mg^{2+} or bicuculline. On the other hand, pharmacological concentration of 1 μmol/l enhanced the frequency of epileptiform ac-

tivity in experiments performed during the day. This effect was suppressed through simultaneous administration of the melatonin receptor antagonist luzindole (10 μM/l). In contrast, melatonin did not affect epileptic activity in slices prepared at night. Additionally, in the bicuculline model, the hormone did not affect epileptiform discharges elicited either during the day or at night. This may suggest that melatonin affects epileptiform discharges in a diurnal manner and that this action is dependent on the type of epilepsy model [59].

Human studies (melatonin effects in clinical studies)

Anticonvulsant properties

Currently, only a few small scale trials of adjunctive melatonin administration in humans have indicated that melatonin may decrease the incidence of seizures. Clinical observation demonstrated improvement in seizure activity in five of six children with intractable seizures who were treated with 3 mg of oral melatonin as a supplement to their conventional AED treatment regimen. Seizure activity has been reported to return to pretreatment levels after discontinuing melatonin treatment in all patients [64].

Some studies have shown that melatonin may be effective in counteracting drug-resistant seizures in children. Molina-Carballo [54] observed a female child who began to have convulsive seizures at the age of 1.5 months, and was diagnosed as having severe myoclonic epilepsy. She was unsuccessfully treated with different combinations of anticonvulsants, including valproic acid, phenobarbital, clonazepam, vigabatrin, lamotrigine, and clobazam. After 1 month of melatonin (50 mg nightly) plus phenobarbital therapy and for a year thereafter, the child's seizures were under control. Reduction of the dose of melatonin led to destabilization of the patient's condition, which was in turn re-stabilized after restoring melatonin [54].

Another double-blind, placebo-controlled study in epileptic children assessed the effects of add-on melatonin administration on their quality of life. Improved physical function, emotional well-being, cognitive function, social function, and behavior suggested that melatonin might be an advantageous adjunctive drug in epileptic patients [34].

Bazil et al. [7] reported that patients with intractable epilepsy have low baseline salivary melatonin levels, which increase significantly following seizures. A lack of sufficient concentrations of melatonin in such individuals could thereby facilitate seizures. Moreover, an increased melatonin level after seizures may be protective against repetitive seizures [7]. Adaptational changes in melatonin concentrations have also been confirmed by other authors. They observed increased excretion of urinary melatonin metabolites in a 24-h period following seizures in patients with active epilepsy. It is interesting that treatment with carbamazepine decreased the urine concentration of melatonin metabolites [75].

Yalyn and co-workers [93] showed no differences in the daily rhythms of melatonin between patients with diurnal complex partial epilepsy, nocturnal complex partial epilepsy, and a control group. All patients were treated with carbamazepine. These results suggest that endogenous melatonin does not contribute to the occurrence of nocturnal complex partial seizures [93].

According to Jones et al. [38] melatonin can alleviate sleep disturbances in young epileptic patients, although without effect on seizures. In another study, six of ten children with sleep disturbances and therapy-resistant epilepsy showed a clear decrease in their seizure frequency under treatment with melatonin (five children received 10 mg and one child received 5 mg). The authors concluded that the observed improvement could be due to both a reduction of sleep deprivation consequences and the anticonvulsant action of melatonin.

Fauteck et al. [28, 29] suggested that melatonin can suppress neuronal epileptic activity *via* specific neocortical melatonin receptors. Additionally, the indoleamine increases the release of prolactin, which in turn enhances GABA neurotransmission [5, 28].

Proconvulsant properties

Sandyk [73] reported that melatonin may also exert proconvulsant effects in humans. It was previously stated that melatonin at low doses increases hypothalamic and cortical GABA levels, accounting for its anticonvulsant action, but that at higher doses it decreases GABA concentrations in these structures. In humans, treatment with melatonin increased α rhythm and induced electroencephalographic abnormalities in patients with temporal lobe epilepsy and intractable epilepsy. According to the author, the proconvulsive properties of melatonin may explain the increased occurrence of seizures at night, when melatonin plasma

levels are 5 to 8-fold higher than during the day [73]. However, these conclusions were not confirmed by other researchers.

In another study, Sheldon [76] showed proconvulsant effects of oral melatonin (5 mg) in neurologically disabled children. Increased seizure frequency was noted 13 days after the onset of therapy and returned immediately to baseline after discontinuing treatment [76].

Conclusions

The majority of data indicate anticonvulsant properties of melatonin when applied at pharmacological doses in both animal models and clinical investigations. However, the studies described in the review were conducted in different animal models, with different melatonin doses and routes of administration. Therefore, it is difficult to reach unambiguous conclusions. It is also too early to recognize melatonin as a potential drug candidate for add-on therapy in epileptic patients. More reliable double-blind, placebo-controlled studies are needed to confirm such a supposition. Presently, melatonin application may be considered when epilepsy co-exists with insomnia.

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