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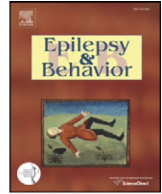

Treatment with melatonin after status epilepticus attenuates seizure activity and neuronal damage but does not prevent the disturbance in diurnal rhythms and behavioral alterations in spontaneously hypertensive rats in kainate model of temporal lobe epilepsy

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ABSTRACT

Melatonin is involved in the control of circadian and seasonal rhythmicity, possesses potent antioxidant activity, and exerts a neuroprotective and anticonvulsant effect. Spontaneously hypertensive rats (SHRs) are widely accepted as an experimental model of essential hypertension with hyperactivity, deficient sustained attention, and alterations in circadian autonomic profiles. The purpose of the present study was to determine whether melatonin treatment during epileptogenesis can prevent the deleterious consequences of status epilepticus (SE) in SHRs in the kainate (KA) model of temporal lobe of epilepsy (TLE). Spontaneous recurrent seizures (SRSs) were EEG- and video-recorded during and after the treatment protocol. Melatonin (10 mg/kg diluted in drinking water, 8 weeks) increased the seizure-latent period, decreased the frequency of SRSs, and attenuated the circadian rhythm of seizure activity in SHRs. However, melatonin was unable to affect the disturbed diurnal rhythms and behavioral changes associated with epilepsy, including the decreased anxiety level, depression, and impaired spatial memory. Melatonin reduced neuronal damage specifically in the CA1 area of the hippocampus and piriform cortex and decreased hippocampal serotonin (5-HT) levels both in control and epileptic SHRs. Although long-term melatonin treatment after SE shows a potential to attenuate seizure activity and neuronal loss, it is unable to restore epilepsy-associated behavioral abnormalities in SHRs.

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1. Introduction

Depression is a common comorbid disorder in epilepsy, but it often remains unrecognized and untreated. Recently, we studied the development of behavioral and neurochemical indices of depressive state in the kainate (KA) model of TLE in two rat strains [1]. The emotional disturbances in epileptic Wistar and SHRs were accompanied by decreased levels of hippocampal serotonin (5-HT) and dopamine (DA). These results were in agreement with the reported compromised serotoninergic neurotransmission in the raphe-hippocampal serotonergic pathway in the pilocarpine post-status epilepticus (SE) model [2]. One factor, which may contribute to the development of depressive state in TLE is rhythm disturbances and, in particular, phase changes in melatonin synthesis. It is widely accepted that mood disorders are related to biological rhythm abnormalities, which can include diurnal mood variation, elevated nocturnal body temperature, lower nocturnal thyroid-stimulating hormone, an overall increased cortisol secretion, and sleep architecture abnormalities as well as an increase in cortisol and melatonin secretion [3]. Products active on circadian rhythms are shown to have chronobiotic effects, and exogenous melatonin is considered one of the best-known

Abbreviations: ABP, arterial blood pressure; BL, basolateral nucleus; C, control; DA, dopamine; DNA, deoxyribonucleic acid; DWRME, “double” working and reference memory error; EEG, electroencephalography; EPM, elevated plus maze; FST, forced swimming test; 5-HT, serotonin; Hip, hippocampus; HPLC, high-performance liquid chromatography; i.p., intraperitoneally; KA, kainic acid; Mel, melatonin; OF, open field; Pir, piriform cortex; PT, pars tuberalis; RAM, radial arm maze; RME, reference memory error; s.c., subcutaneously; SCN, suprachiasmatic nucleus; SCT, sucrose consumption test; SE, status epilepticus; SHRs, spontaneously hypertensive rats; SRSs, spontaneous recurrent seizures; SWDs, spike–wave discharges; TLE, temporal lobe epilepsy; Veh, vehicle; WM, working memory error.

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chronobiotic molecules [4]. Besides its primary function as a synchronizer of the biological clock [5], melatonin is a powerful antioxidant that can easily cross cell membranes and the blood–brain barrier. The accumulated clinical and experimental data raise the point about the potential therapeutic role of melatonin in epilepsy. It has been suggested that a lack of sufficient concentrations of melatonin in patients with epilepsy predisposes them to seizure activity, while adaptive increase of melatonin levels may be protective against repetitive seizures [6]. Clinical evidence revealed that melatonin could be used for seizure control in conjunction with antiseizure medications [7].

Intact SHRs represent a useful model to explore mechanisms underlying disturbed circadian synchronization [8,9]. The disturbances of physiological circadian rhythms underline also a number of impaired processes, some of them resulting in cardiovascular diseases. Therefore, the melatonin system is a good candidate strategy for the treatment of circadian timing system disturbance. Cerebrovascular changes, brain atrophy, loss of nerve cells in cerebrocortical areas, and glial reaction were documented in this strain (reviewed in [10]). In chronic models of epilepsy, SHRs are reported to kindle more rapidly than Wistar Kyoto rats in amygdala and piriform kindling [11]. It is documented that the enhanced seizure susceptibility observed in the pilocarpine model of TLE correlates with neuropathological alterations in the hippocampal formation of SHRs [12]. Clinical data showed disturbances of melatonin biosynthesis in patients with hypertension [13], while experimental studies reported an antihypertensive effect of melatonin in SHRs [14,15]. Taken together, these data are in agreement with the idea that melatonin may have potential for preventing neuronal damage after brain insults such as brain trauma and cerebral ischemia-induced SE, including hypertension-evoked brain damage. Acute administration of melatonin in rats before and during SE induced by either KA or pilocarpine displays neuroprotective effects by reducing neuronal death, supragranular mossy fiber sprouting, lipid peroxidation, and microglial activation [16–18].

Recently, we reported that unlike in the epileptic Wistar rats, which were characterized with depressive behavior only during the light phase, depressive-like patterns were without diurnal variations in epileptic SHRs [1]. Furthermore, the long-term administration of melatonin alleviated the seizure activity during the period of treatment, decreased the neuronal loss in the hippocampus and the piriform cortex, and exerted changes in the behavioral responses specifically during the inactive period in the chronic epileptic phase of normotensive Wistar rats [19]. The important function of melatonin in the circadian timing system and epileptic phenomena, on the one hand, and the significance of synchronization of circadian rhythms both in epilepsy and depression, on the other hand, prompted us to further explore whether long-term melatonin treatment after SE could alleviate the deleterious consequences of SE and the diurnal behavioral disturbances during the chronic epileptic state in SHRs.

2. Material and methods

All experiments were executed in compliance with the European Communities Council Directive of 24th November 1986 (86/609/EEC), and the experimental design was approved by the Institutional Ethics Committees of Sofia Medical University and the Institute of Neurobiology for the National Science Fund grant DTK 02/56 2009-1012.

2.1. Subjects

The experiments were performed on eight-week-old male spontaneously hypertensive rats (SHRs) obtained from the local breeding house (Medical University, Sofia). Following their arrival in the laboratory, the animals were habituated for one week (12/12-h light/dark cycle, lights on at 08:00 h), individually housed under standardized conditions (20 ± 3 °C, 40–60% relative humidity), and handled daily. Food and water were available ad libitum throughout the study except during the tests. All experiments were carried out in the autumn–winter season.

2.2. Experimental design and drug treatment

Animals were randomly divided into four main groups: C-veh (control group treated with vehicle, n = 15); C-mel (control group treated with melatonin, n = 15); KA-veh (rats treated with KA and vehicle, n = 16); and KA-mel (rats treated with KA and melatonin, n = 17). Treatment with melatonin (Sigma-Aldrich, Bulgaria) started 3 h after the beginning of SE at a dose of 10 mg/kg, previously shown to have neuroprotective and antioxidant activities [20]. During the first three days, when the animals were unable to drink via bottles, melatonin was injected subcutaneously (s.c.), dissolved in a lactated Ringer's solution (2 ml/100 g of body weight/day, s.c.). Matched animals not treated with KA were also injected with melatonin or vehicle during the first three days. Later, melatonin was diluted in the drinking water for a period of 8 weeks. Control rats were given tap water. Daily preparation of drinking water containing melatonin was adjusted dependent on the individual consumed volume of a liquid. Behavioral tests started about 14 weeks after SE, when the rats developed a stable chronic epileptic state. The time interval between each test was at least 2 days. The order of the behavioral tests was as follows: open-field (OF) test, elevated plus maze (EPM) test, and forced swimming (FS) test. Ten days after the last testing, rats were tested with the radial arm maze (RAM) test to evaluate whether the chronic melatonin treatment was able to improve learning disability of epileptic rats in a hippocampal-dependent spatial task.

2.3. Surgery

Four rats from the KA-veh group and the KA-mel group were monitored for electrographic seizures affecting the frontal and parietal cortices and the dorsal hippocampus using either epidural or depth chronic recordings. Electrodes for electroencephalography (EEG) recording were implanted on the rats under a mix of ketamine (40 mg/kg) and xylazine (20 mg/kg, intraperitoneally (i.p.)) anesthesia. The animals were placed on a rectal temperature feedback-controlled pad (Digitherm, Yukon-PC, Sofia, Bulgaria), which maintained body temperature at 37 °C. Following local anesthesia with procaine 0.5% and fixation in a stereotaxic device (Narishige Sci. Inst. Labs, Japan), a midline incision over the skull was made, and the skin and the periosteum were removed with aseptic precautions. For monopolar EEG recordings, pieces of teflon-coated (275 μm) stainless steel wire (Medwire Corp, N.Y.) were inserted into premade small holes in the calvaria bilaterally of both hemispheres above the parietal cortical areas (A = −4.2, L = ±3.0). For the hippocampal electrodes, we used two sets of twisted wires, from which the tips were separated vertically by 1 mm and inserted into the left and the right hemispheres with the coordinates for the dorsal hippocampus as follows: A = −4.0, L = ±2.5, and H = −3.3. The other ends of the wires were soldered to the pins of a female miniature socket. Two miniature stainless steel screws, one fixed on the skull above the frontal bone and the other posterior to the lambda, were used for ground and common references, respectively. All wires and screws were covered and fixed to the skull with dental acrylic cement. The two screws served also for anchoring the cement mound to the skull. The rats recovered after the surgery for about one week, during which they were handled once daily and then placed in a recording cage for habituation. Recording of control EEG (before the KA treatment) started 7 days after the surgery and was performed on entirely conscious rats. The female connector fixed on the animal's head was matched with a male connector, to which a flexible shielded cable was soldered. The opposite end of the cable was connected to a swivel commutator mounted on the box's ceiling allowing EEG to be recorded continuously in awake, unrestrained animals. The output of the connector was fed to a Nihon Kohden electroencephalograph (Japan), and EEG was recorded by means of the

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