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The reducing effect of agomelatine on pentylenetetrazol-induced convulsions

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Introduction: Agomelatine is a potent MT1 and MT2 melatonin receptor agonist and a 5-HT2C serotonin receptor antagonist. The purpose of this study was to show the convulsion-reducing effect of agomelatine, in both clinical and electrophysiological terms, in a pentylenetetrazole (PTZ)-induced experimental epilepsy model in rats. *Methods:* The anti-convulsant activity of agomelatine (25 and 50 mg/kg) was evaluated in rat models of PTZ (35 and 70 mg/kg) and compared with the control groups. *Results:* Agomelatine administration at doses of 25 and 50 mg/kg resulted in a statistically significant decrease in convulsion scores and time to onset of myoclonic jerks compared to the control groups. In addition, comparison of the two doses employed showed that high-dose agomelatine (50 mg/kg) was significantly more effective than the lower dose. In addition to previous studies, we investigated the anticonvulsant effect of agomelatine using electroencephalogram (EEG). Administration of agomelatine at doses of 25 and 50 mg/kg in PTZ-induced seizures caused a significant decrease in the percentage of peak at EEG. *Discussion:* Our results suggest that agomelatine has anticonvulsant activity shown in PTZ-induced seizure model. The results also give some evidences that agomelatine can use on epileptic seizures, but more studies are needed.

Original Article

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INTRODUCTION

Epilepsy is a chronic neurological disease occurring with an excessive discharge or neurons and characterized by recurrent, spontaneous seizures (Strine et al., 2005). The reported prevalence is 0.5%–1%, although the lifetime prevalence may rise to approximately 3% (Hauser et al., 1993). Treatment is long term and generally lifelong. Although antiepileptic agents halt seizures and reduce their frequency, approximately 30% of epilepsy cases are resistant to treatment (Brodie & Ditcher, 1996). In addition to classic antiepileptic therapeutic options that have been used for many years and are quite effective, such as phenytoin, carbamazepine, valproic acid, and lamotrigine, a wide range of new generation antiepileptics are also available, including levetiracetam, topiramate, zonisamide, and lacosamide. However, in addition to the effectiveness of these options, they are also capable of producing various metabolic, psychiatric, and behavioral side effects (Dastgheib & Moezi, 2014; Erbas et al., 2015).

Agomelatine entered the market in 2009, and its multifaceted side effects have been examined in several recent experimental studies (Boulle et al., 2016; Karamustafalıoglu & Baran, 2012; Mairesse et al., 2013; Morley-Fletcher et al., 2011; Rainer et al., 2012; Uzbay, 2012). Agomelatine is a melatonin receptor agonist that binds to and stimulates the MT1 and MT2 receptors in the suprachiasmatic nucleus. Simultaneously, as a5-HT2c receptor antagonist, it prevents the activities of receptor subtype activities (Dastgheib & Moezi, 2014; Karamustafalıoglu & Baran, 2012; Uzbay, 2012). Agomelatine has been shown to exhibit positive effects on depression, anxiety, sleep disorders, the circadian rhythm, and cognition in several animal studies and in human patients (Comai & Gobbi, 2014). Data concerning the effectiveness of the drug in daily life are promising.

In addition to the known effects of agomelatine, research has also investigated its potential anticonvulsive properties, and positive effects have been shown in several studies (Aguiar et al., 2012; Dastgheib & Moezi, 2014). However, the effect

mechanism is still not entirely clear, and this continues to be the subject of research. The purpose of this study was to show the convulsion-reducing effect of agomelatine, in both clinical and electrophysiological terms, in a pentylenetetrazole (PTZ)-induced experimental epilepsy model in rats.

MATERIALS AND METHODS

Animals and laboratory

The experimental procedures employed in this study were approved by the local animal ethics committee. All experiments were carried out in line with the Guide for the Care and Use of Laboratory Animals, as confirmed by the US National Institutes of Health.

Forty-eight male Sprague–Dawley rats [24 for electroencephalogram (EEG) recording (Group A) and 24 for behavioral (Group B) studies] weighing 200–250 g were used in this study. The rats were kept in a 12-hr dark–light cycle (light from 07.00 to 19.00), in quiet rooms, at a 22–24 °C ambient temperature. All animals were allowed *ad libitum* access to standard laboratory chow and tap water.

Experimental procedures

Rats were randomly divided into two groups: Group A for EEG recordings and Group B for behavioral assessment. Rats in Group A were placed under deep anesthesia, and small hole was opened using a drill under stereotaxic conditions. Electrodes (polyamide-coated stainless steel wires, 0.1 mm diameter with electrical resistance <1/10 mm) were implanted in the dura over the left frontal cortex (2.0 mm lateral to the midline and 1.5 mm anterior to the bregma), while the reference electrode was implanted over the cerebellum (1.5 mm posterior to the lambda, on the midline) (9, 10) for EEG recording. The electrodes were then fixed in place using dental acrylic (a mixture of numerous alloys used for dental restoration). Rats were placed under deep anesthesia by intraperitoneal (i.p.) administration of ketamine (80 mg/kg) and xylazine (4 mg/kg).

Twelve days after electrode fixation, the 24 rats were divided randomly into four subgroups ($n = 6$): A1, A2, A3, and A4.

Group A1 was defined as the control group and received no medication. Group A2 was administered with saline solution i.p., Group A3 received 25 mg/kg agomelatine i.p. (Valdoxan, 25 mg/ml, Servier, Istanbul/Turkey), and Group A4 received 50 mg/kg agomelatine i.p. The drugs were administered 30 min prior to PTZ (35 mg/kg, i.p.) injection. All groups, with the exception of Group A1, received 35 mg/kg PTZ, and EEG was recorded. EEG recordings were taken with the rats awake and in a special container 5 min after PTZ administration. A dose of 35 mg/kg is ideal for observing changes in EEG spikes but does not consistently produce observable behavioral changes, while 70 mg/kg consistently produces observable behavioral changes, therefore two different doses were admitted in the study (A and B groups).

In summary, the EEG recordings were taken for 60 min, and the signals were amplified 10,000 times and filtered within a range of 1–60 Hz. The EEG records were obtained using the BIOPAC MP150 Data Acquisition System (Biopac System Inc., Santa Barbara, CA, USA), and spike percentages were evaluated. Two clinical neurophysiologists scored the EEG data in terms of spike percentages (a reproducible way of quantifying epileptiform activity to calculate the percentage of 1-s bins with at least one spike-wave, known as the "spike-wave percentage"). The onset and cessation of this complex were identified by a higher amplitude (at least twofold) compared with baseline values. The cumulative duration of the spike wave was detected over 2-min intervals.

The remaining 24 rats (Group B) were also divided into four subgroups ($n = 6$): B1, B2, B3, and B4. The first (Group B1) was defined as the *control* group and received no medication. Group B2 was administered with saline i.p., Group B3 received 25 mg/kg agomelatine i.p., and Group B4 received 50 mg/kg agomelatine i.p. The drugs were administered 30 min prior to PTZ (70 mg/kg, i.p.) injection. Racine convulsion scores (RCSs; Vimala et al., 2014) and onset times of the "first myoclonic jerk" (FMJ) were used to evaluate the seizures (for PTZ 70 mg/kg only) under the following classification: 0 = no convulsion; 1 = twitching of vibrassae and pinnae; 2 = motor arrest with more pronounced twitching; 3 = motor arrest with generalized myoclonic jerks (this time was recorded to evaluate the FMJ onset time); 4 = tonic clonic seizure with the animal remaining on its feet; 5 = tonic–clonic seizure with loss of the righting reflex; 6 = lethal seizure. Rats were observed for onset times of FMJ as previously described (Erbas et al., 2015). The onset times were recorded in the form of seconds. Almost all animals exhibiting tonic generalized extension died. The observation period for PTZ-induced seizures was limited to 30 min (Erbas et al., 2015), after which the animals were euthanized.

Statistical analyses

The results were expressed as mean ± standard error of mean. Data analyses were performed on SPSS version 15.0 (Chicago, USA) for Windows software. The Shapiro–Wilk test was used to determine if a population of values exhibited normal distribution. RCS were evaluated using the Kruskal–Wallis test, and FMJ times were evaluated using one-way analysis of variance. The *post-hoc* Bonferroni test and Mann–Whitney *U* test were utilized to identify differences between the experimental groups. The values of $p < .05$ were regarded as statistically significant.

RESULTS

Behavioral seizure analysis

Comparison of the PTZ (70 mg/kg) and 25 mg/kg agomelatine-treated group (Group B3) with the PTZ (70 mg/kg) and saline group (Group B2) revealed a significantly lower RCS in the agomelatine-treated group ($p < .001$). RCS was also lower in the PTZ (70 mg/kg) and 50 mg/kg agomelatine-treated group (Group B4) compared

Table 1. Effects of agomelatine in the seizure model induced by PTZ in mice

Drug group	Convulsion stage (Racine)	FMJ onset time (s)
B1 – Control	0	0
B2 – PTZ (70 mg/kg) and saline	5.5 ± 0.2	69.5 ± 3.9
B3 – PTZ (70 mg/kg) and 25 mg/kg agomelatine	2.66 ± 0.4*	181.6 ± 36.8*
B4 – PTZ (70 mg/kg) and 50 mg/kg agomelatine	1.8 ± 0.2*	244.3 ± 19.5*

Note. FMJ: first myoclonic jerk; PTZ: pentylenetetrazol.
*$p < .001$, PTZ (70 mg/kg) and 25 mg/kg or 50 mg/kg agomelatine group compared with the PTZ (70 mg/kg) and saline group.

with the PTZ (70 mg/kg) and saline group (Group B2). Lower RCS was also observed in the PTZ (70 mg/kg) and 50 mg/kg agomelatine-treated group than in the PTZ (70 mg/kg) and 25 mg/kg agomelatine-treated group ($p = .005$; Table 1).

Time to onset of FMJ was significantly longer in the PTZ (70 mg/kg) and 25 mg/kg agomelatine group (Groups B3 and B4) than in the PTZ (70 mg/ kg) and saline group (Group B2; $p = .00001$). Time to onset of FMJ was longer in the PTZ (70 mg/kg) and 50 mg/kg agomelatine-treated group than in the PTZ (70 mg/kg) and 25 mg/kg agomelatine group ($p = .005$; Table 2).

Electrophysiological evaluation

Evaluation of spike percentages in Group A revealed significantly lower mean spike percentages values in the PTZ (35 mg/kg) and 25 and 50 mg/kg agomelatine-treated groups (Groups A3 and A4) than in the group receiving PTZ (35 mg/kg) and saline (Group A2; $p = .001$; Table 2). Mean spike percentage values were lower in the PTZ (70 mg/kg) and 50 mg/kg agomelatine-treated group (Group A4) than in the PTZ (70 mg/kg) and 25 mg/kg agomelatine group (Group A3; $p = .005$; Fig. 1).

Table 2. Comparison of Spike percentages of the groups

Drug group	Spike (%)
A1 – Control	0
A2 – PTZ (35 mg/kg) and saline	70.8 ± 6.3
A3 – PTZ (35 mg/kg) and 25 mg/kg agomelatine	28.5 ± 5.4*
A4 – PTZ (35 mg/kg) and 50 mg/kg agomelatine	16.1 ± 2.8*

Note. PTZ: pentylenetetrazol.
*$p < .001$, PTZ (35 mg/kg) and 25 mg/kg or 50 mg/kg agomelatine group compared with the PTZ (35 mg/kg) and saline group.

DISCUSSION

Agomelatine (β-methyl-6-chloromelatonin) is a MT1 and MT2 receptor agonist, and a5-HT2c receptor antagonist (Aguiar et al., 2012; Dastgheib & Moezi, 2014; Karamustafalioglu & Baran, 2012; Uzbay, 2012). Tchekalarova et al. (2016) showed that chronic agomelatine injection in rats subjected to pinealectomy protected the hippocampus, septal dentate gyrus, temporal piriform cortex, and basolateral amygdala against neuronal damage (Tchekalarova et al., 2016). In addition to this neuroprotective role, Tchekalarova et al. (2017) also suggested that it is capable of suppressing epileptogenesis by protecting certain cerebral structures. In that study investigating the effects of agomelatine on epileptogenesis in status epilepticus (SE) and on behavioral and neuronal damage, agomelatine (40 mg/kg, i.p.) was started 1 hr after SE in Wistar rats and was continued for 10 weeks. Spontaneous motor seizures and locomotor activity were observed, and cognitive functions were also evaluated with memory tests. They showed that agomelatine delayed the onset of spontaneous motor seizures in the second and third weeks and reduced the frequency of seizures. Chronic agomelatine therapy exhibited a neuroprotective effect in the dorsal hippocampus, the hilus of the dentate gyrus, the piriform cortex, and temporal basolateral amygdala, but had no effect on the ventral hippocampus, dentate gyrus, or entorhinal cortex. They reported that this selective effect in different regions of the brain might account for the insufficient effects of agomelatine on seizure epileptogenesis and behavioral responses including anxiety and memory (Tchekalarova et al., 2017).

Pentylenetetrazol is a classic gamma-aminobutyric acid (GABA) receptor antagonist. It exhibits its epileptic effect by binding in the picrotoxin region of the GABA receptor complex and blocking GABA-mediated inhibition. In addition, PTZ causes epileptic seizures to be generalized by activating NMDA receptors (Moezi et al., 2011; Olsen et al., 1981; Velisek, 2106). PTZ intravenous (i.v.) infusion triggers myoclonic and absence seizures in the face and the body, and i.v. administration of PTZ is known to be more sensitive than i.p. PTZ administration (Durlach-Misteli & Van Ree, 1992).

The anticonvulsant effect of agomelatine in seizures induced by pilocarpine and PTZ in female rats was first shown by Aguiar et al. (2012). Their study showed a prolongation of convulsion latency using agomelatine at a dosage of 25–50 mg/kg in PTZ-induced seizures, whereas prolongation in convulsion latency at high doses (50–75 mg/kg) could result in fatal prolongation. The authors reported that agomelatine exhibits its anticonvulsant effect by way of GABAergic mechanisms. In addition, only high doses of agomelatine (75 mg/kg) led to prolongation in convulsion latency and a fatal course in pilocarpine-induced seizures. No effect of agomelatine has been shown in seizures induced using other methods (strychnine, electroconvulsive therapy, or picrotoxin; Aguiar et al., 2012). In another study, Dastgheib and Moezi (2014) investigated the chronic and acute effects of agomelatine in PTZ-induced seizures in male rats. Agomelatine was administered in the acute period [12.5, 25, 50, 75, and 100 mg/kg per oral (p.o.)] and the chronic period (25, 50, and 75 mg/kg p.o., once daily for 7 days). Nitric oxide synthase (NOS) inhibitors (L-NAME), iNOS inhibitors (aminoguanidine), and nNOS inhibitors (7-nitraindazol) and agomelatine (50 and 75 mg/kg) were used to investigate the effect between the anticonvulsant

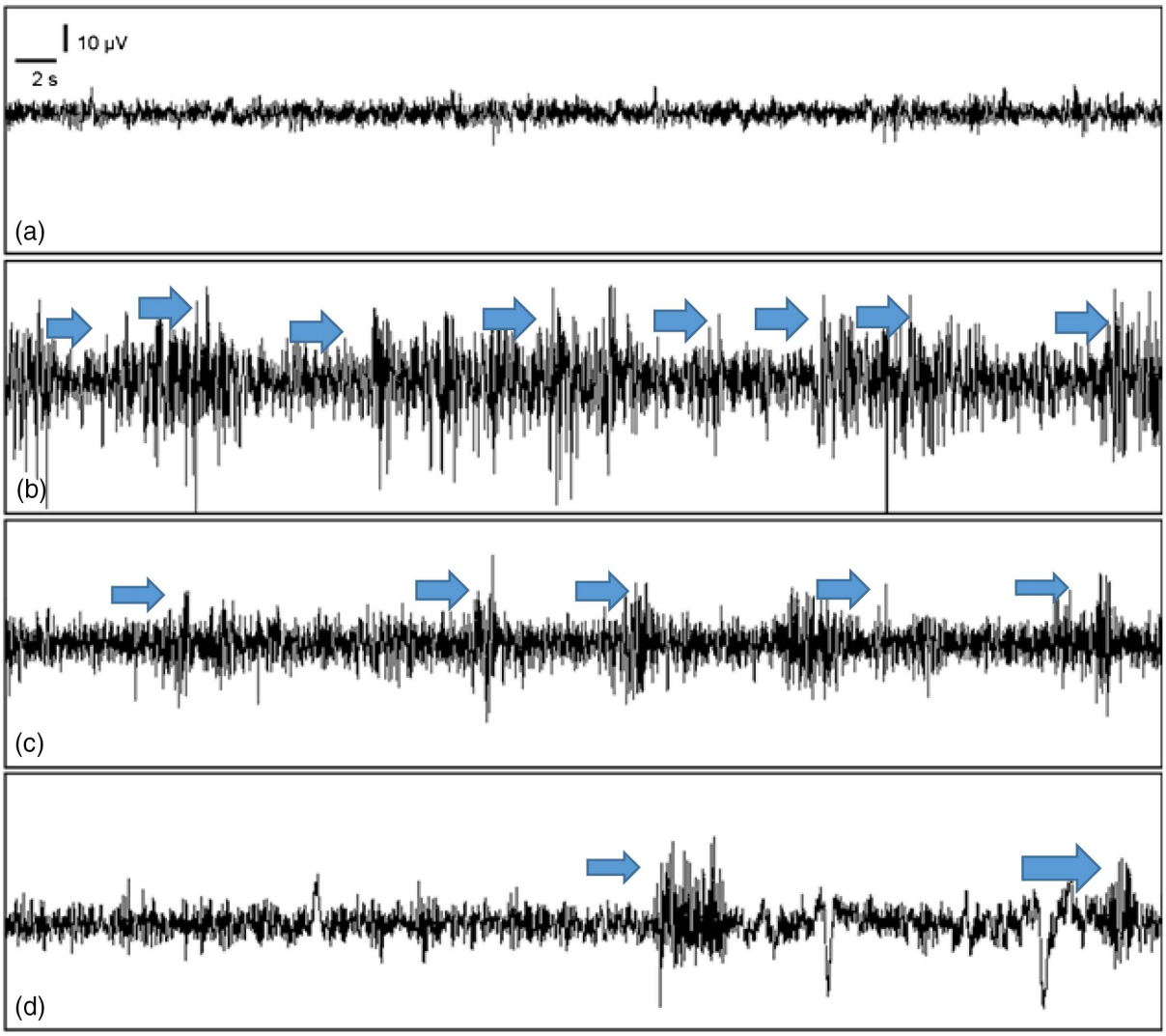

Fig. 1. EEG recording. (a) Control group, (b) PTZ (35 mg/kg) and saline group, (c) PTZ (35 mg/kg) and 25 mg/kg agomelatine group, (d) PTZ (35 mg/kg) and 50 mg/kg agomelatine group

effect of agomelatine and nitric oxide. Acute administration of agomelatine produced an increase in the threshold of clonic seizures, while no significant response was achieved with chronic administration. The authors reported that findings show that agomelatine is effective in the acute period but not in the chronic period, and that this may be explained in terms of receptor desensitization. That study also reported that the administration of agomelatine together with NO inhibitors protected against the anticonvulsant effect of agomelatine and that the NO pathway played a role in the anticonvulsant effect (Dastgheib & Moezi, 2014). Studies have described the anticonvulsant effectiveness of agomelatine through both GABA and NO (Aguiar et al., 2012; Dastgheib & Moezi, 2014; Tchekalarova et al., 2017; Vimala et al., 2014).

In the light of the above information, the purpose of this study was to show the anticonvulsant effect of agomelatine, using both clinical and electrophysiological findings, in an experimental epilepsy model established using i.p. PTZ. Agomelatine administration at doses of 25 and 50 mg/kg resulted in a statistically significant decrease in convulsion scores and time to onset of myoclonic jerks compared to the control groups (for Group A). In addition, comparison of the two doses employed showed that high-dose agomelatine (50 mg/kg) was significantly more effective than the lower dose.

In addition to previous studies, we investigated the anticonvulsant effect of agomelatine using EEG (for Group B). Administration of agomelatine at doses of 25 and 50 mg/kg in PTZ-induced seizures caused a significant decrease in the peak percentage at EEG. Comparison of the two doses showed that agomelatine caused a greater decrease in peak percentages at the higher dosage. Although the anticonvulsant effect of agomelatine has been shown in other previous studies (Aguiar et al., 2012; Dastgheib & Moezi, 2014; Tchekalarova et al., 2017; Vimala et al., 2014), this is the first study to show the improving effect both at EEG findings and clinical convulsion scores.

In conclusion, as an antidepressant and an anxiolytic, agomelatine exhibits anticonvulsant effects in both EEG and clinical terms in the acute period. Comorbidity of depression and anxiety disorder with epilepsy is a commonly encountered problem for both the patient and the clinician. For that reason, it is essential that the clinicians consider the probable effect on epileptic seizures before initiating an

antidepressant or anxiolytic agent. Furthermore, real-life data and longitudinal studies are needed to determine the effect of long-term agomelatine use on epileptic seizures, cognition, and cerebral structures.

CONCLUSION FOR FUTURE BIOLOGY

The results of this study indicate that agomelatine has an anticonvulsant activity in animal models induced by PTZ, and this action may be related to GABAergic mechanisms. The anticonvulsant effect of agomelatine has been shown in other previous studies. To the best of our knowledge, this is the first study to show the improving effect both at EEG findings and clinical convulsion scores. The results also give some evidences that agomelatine can use on epileptic seizures, but more studies are needed.

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Ethical Statement: All experiments, performed in the study, were carried out according to the rules in the Guide for the Care and Use of Laboratory Animals, as adopted by National Institutes of Health (USA) and received the Ege University Animal Ethics Committee's consent (2011-187).

Competing Interests: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contributions: EAD and BPC contributed in planning and writing this study. MAE involved in planning and performed studies on experimental rat model. OE performed studies on experimental rat model.

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