RESEARCH PAPER

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The effect of Madopar on absence-like seizures in WAG/Rij rats

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The aim of this study was to investigate the effect of Madopar on the absence seizures and the anxiety-like behavior (assessed using the open field test) in Wistar Albino Glaxo/Rijswijk (WAG/Rij) rats. Twenty-eight male WAG/Rij rats were randomly divided into four groups: group I: control; group II: Madopar 5 mg/kg; group III: Madopar 50 mg/kg; group IV: Madopar 100 mg/kg. A tripolar electrode was attached to all WAG/Rij rats. Electrocorticography (ECoG) recordings were made before and after Madopar (5, 50, and 100 mg/kg) injection for three hours. Anxiety-related behavior was studied using the open field test for 5 min after the ECoG recordings. Madopar significantly reduced the number and duration of spike-wave discharges (SWDs) when compared to the control group. The highest dose of Madopar (100 mg/kg) significantly reduced the duration of SWDs when compared to Madopar (5 mg/kg). All Madopar doses did not alter the duration of grooming, but the highest doses of Madopar significantly increased the number of squares crossed in the open field test when compared to the control and Madopar (5 mg/kg) groups. These results revealed that Madopar reduced the absence-like seizures and the anxiety-related behavior in WAG/Rij rats. This may emphasize the therapeutic properties of the Madopar/L-dopa in absence epilepsy.

Key words: Madopar, dopamine system, L-dopa, absence-like seizures, WAG/Rij rat

INTRODUCTION

Epilepsy is one of the most frequent neurological conditions, affecting over 70 million people worldwide, and it comes in various types and levels of severity (Ngugi et al., 2010). Still, there is no definitive treatment to cure the cause, and about 30% of patients' epileptic seizures cannot be controlled by medicines (Fisher et al., 2005; Löscher and Schmidt, 2011). Moreover, around 80% of the epileptic patients live in low- and middle-income nations, with approximately 75% without therapy (Saxena and Li, 2017). The unstable quality of life and enhanced risk of premature death, sensory, behavioral, psychological, psychiatric, and social illnesses in many patients has resulted from the uncertain nature of epilepsy (Fisher et al., 2005).

Thus, finding new alternatives is mandatory to overcome uncontrollable seizures. From the last century, approximately 60 years ago, there was evidence of anticonvulsant activity linked to D2 receptor stimulation, while the stimulation of the D1 receptor might have a proconvulsant effect by lowering the midbrain convulsion threshold (Starr, 1996). More recently, researchers have assessed whether there is a dopaminergic mechanism that can control seizures. Quesney et al. (1980) demonstrated that the administration of apomorphine (dopamine receptors agonist) considerably decreased or even blocked photo-induced seizures. Moreover, the seizures may be exacerbated with the administration of anti-dopaminergic drugs (Rektor et al., 2012). Positron emission tomography has helped to determine that idiopathic generalized epilepsy is also accompanied by changes in the dopamine system

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(Ciumas et al., 2010), and the distribution of dopamine receptors in absence epilepsy is severely affected (Birioukova et al., 2005). Birioukova et al. (2016) revealed that there is a reduction in the density of the dopaminergic system in the substantia nigra pars compacta in WAG/Rij rats (absence epilepsy model), but in the epileptogenesis phase, there are an increased density of D2 receptors.

Levodopa (L-dopa) (L-3,4-dihydroxyphenylalanine) is a naturally occurring amino acid and a dopamine precursor, a neurotransmitter that has been significantly decreased in Parkinson's disease because of neuronal cell degeneration (Fahn and Sulzer, 2004). L-dopa is considered a prodrug that is used as a conventional treatment for Parkinson's disease (Yahr et al., 1969). It is able to cross the blood-brain barrier when administered systemically, then transforms to dopamine through the action of the L-dopa decarboxylase enzyme (Hauser and Zesiewicz, 2007). Slapal and Zouhar (1989) introduced L-dopa to children with refractory Lennox-Gastaut syndrome and the results were very favorable, so they presumed that the L-dopa has a role in the pathogenesis of several epileptic syndromes. Moreover, Hodoba et al. (2013) introduced Madopar to three adult humans with epilepsy, 2 with ultra-refractory focal epilepsy, and one with Lennox-Gastaut syndrome. After receiving the treatment for 6–12 months, the results demonstrated an improvement in controlling the generalized tonic-clonic seizures in focal epilepsy one.

In order to understand the absence epilepsy in humans and its molecular and pathophysiological characteristics, we can use an animal model that simulates the specifications of the absence epilepsy. WAG/Rij rats show most of human absence epilepsy's clinical and electrophysiological features, for example, spike-wave discharges (SWDs) spontaneously occurring, behavioral pauses, and even slight oral-facial twitching may occur (Aygun et al., 2019). However, the function of dopamine and dopaminergic therapy have not been yet addressed in epilepsy. In this study, we investigated the electrophysiological changes and effects on absence epilepsy that accompanied the intraperitoneal administration of Madopar into WAG\Rij rats.

METHODS

Animals

This experiment was applied to 35 male adult (six-month-old) WAG/Rij rats with spontaneous absence epilepsy, weighing between 220-250 grams. The animals were kept under control over 12 h light/dark cycles, with free access to food and water, in a constant temperature range (20±3°C), and one week before the experiment they were permitted to acclimate to the lab. All experimental processes were performed in compliance with the Directive of the European Union (2010/63/EU) and Turkish animal experiment legislation. The protocol for the study was approved by the University of Gaziosmanpasa's local ethics commission (HAYDEK-004)

The animals were divided into four groups, with seven animals (n=7) in each group.

Group 1; control group, animals received normal saline (a solvent); group 2; animals in this group received Madopar 5 mg/kg; group 3; animals in this group received Madopar 50 mg/kg; group 4; animals in this group received Madopar 100 mg/kg.

Surgical procedure

For one day the animals fasted before the surgery. We used 90 mg/kg of ketamine and 10 mg/kg of xylazine to anesthetize the animals. Before the surgery, intraperitoneally (i.p.) 50 mg/kg of ampicillin was injected as prophylaxis. With a length of roughly 3 cm, the scalp was opened in the anteroposterior direction. The bregma was identified and deemed a point of reference (Paxinos and Watson, 2006). With a 1 mm diameter drilling tip, 3 distinct points were drilled into the skull by using an electric drill machine with a stereotaxic frame device. Stainless steel screws were put in touch with membranes. The coordinates were 2 mm anterior and 3.5 mm lateral for the frontal region. For the parietal region, the coordinates were 6 mm posterior and 4 mm lateral. The reference electrode was placed above the cerebellum. Dental acrylic was used for the fixation of the screws. The rats in the control group underwent sham surgery as well. After the surgical procedure, the animals housed individually and were allowed to rest for 1 week before the experiment was performed.

ECoG recordings and analysis

In a registration cage (26 × 18 × 42 cm) the animals were placed separately and linked into recording leads. A baseline ECoG recording for 180 min of all animals were obtained. ECoG recordings were continued for 3 h after the administration of Madopar (ECoG recordings were started at 9:00 AM). During the recordings, the animals were continually observed and freely moving. The ECoG recordings were recorded online then saved into the computer by using AcqKnowledge 3.8 software and the MP-150 multichannel physiological analysis system (BioPac Systems Inc.; USA).

The total number and duration of SWDs for baseline and post-injection recordings were calculated. The percentage of each group was obtained by comparing the total number and duration of SWDs with their baseline recording. Thus, the percentage was found according to the baseline record. The Madopar and control groups were compared for statistical differences in SWDs.

Open field test

The apparatus used for the open field test was a 100 × 100 cm square arena with a 30 cm wall, divided into 64 equal compartments. WAG/Rij rats were placed in the center of the test area, and the number of squares crossed and duration of grooming were recorded. The open field test area was cleaned with 5% alcohol after each rat.

Statistical analysis

The statistical analyses were performed using SPSS 15. One-way ANOVA and then *post hoc* Tukey test were used to compare the groups' results. The results are given as the means±standard error of the mean (SEM). $P<0.05$ was considered statistically significant for all statistical tests.

RESULTS

ECoG recording analysis

The number and duration of the SWDs were calculated before and after the administration of saline and Madopar (5, 50, and 100 mg/kg).

There were no differences in the number and duration of SWDs before and after saline injections. The total number and duration of SWDs were 92.43±7.63; 100.4±7.31 (108.7±7.91%) and 503.9±42.4; 518.0±54.98 (102.8±10.91%) for 180 min before and after the injection of saline, respectively (Fig. 1, 2 and Table 1, 2).

The administration of Madopar (5 mg/kg) led to a significant reduction in the number and the duration of SWDs compared to control recordings. The total numbers and duration of SWDs were 89.43±8.69; 59.43±7.52 (66.46±8.41%) and 490.8±61.97; 321.9±26.60 (65.59±5.42%) for 180 min before and after the injection of Madopar (5 mg/kg), respectively ($P<0.01$; $P<0.01$), (Fig. 1, 2 and Table 1, 2).

The injection of Madopar (50 mg/kg) led to a significant reduction in the number and the duration of SWDs compared to control recordings. The total numbers and duration of SWDs were 102.0±11.21; 63.06±7.64, (63.03±7.63%) and 565.6±71.79; 303.3±41.67 (53.63±7.36%) for 180 min before and after the injection of Madopar (5 mg/kg), respectively, ($P<0.01$; $P<0.01$) (Fig. 1, 2 and Table 1, 2).

The number (44.30±7.97%) and duration (43.11±8.00%) of SWDs after Madopar (100 mg/kg) application was almost 2 times lower than the baseline recordings. Also, the highest doses of Madopar (100 mg/kg) significantly reduced the duration of SWDs when compared to Madopar (5 mg/kg) group ($P<0.05$).

The effects of Madopar in anxiety/depression-like behavior / open field test

The recording was terminated three hours after the Madopar injection. Then, the open field test was applied for 5 min. After acute (5, 50 and 100 mg/kg, i.p.) administration of Madopar in WAG/Rij rats, no statistically significant effects were detected on duration of grooming (11.33±3.42, 100%; 11.83±4.66, 98.28%; 14.00±5.30, 116.3%; 15.01±4.37, 124.6%, respectively) (Table 3) in the open field test when compared to the control group (Fig. 3B). In the 100 mg/kg Madopar group, there was a significant increase in the number of the squares crossed in the open field test when compared to the control group and 5 mg/kg Madopar group, but there was no significant difference compared to the 50 mg/kg group (Fig. 3A). The number of the squares crossed in the control, 5, 50 and 100 mg/kg Madopar groups were 48.67±9.14 – 100%; 42.33±9.00 – 87.41%; 52.00±12.19 – 107.4%; 78.33±7.52 – 161.8%, respectively, 180 min after Madopar injection (Table 3). This study showed that the highest doses of Madopar treatment increased locomotor activity in the open field test.

DISCUSSION

Madopar appeared to have a potent effect on the reduction in the number and duration of SWDs in WAG/Rij rats. Madopar at doses of 5, 50 and 100 mg/kg/i.p. reduced the number and duration of SWDs. The highest Madopar dose (100 mg/kg) had the greatest reducing effect on SWD duration even when compared to the Madopar (5 mg/kg) group. In the open field test, the administration of Madopar had no effect on the duration of grooming, while 100 mg/kg of Madopar increased the number of squares crossed in the open field test when compared to the control and 5 mg/kg Madopar groups.

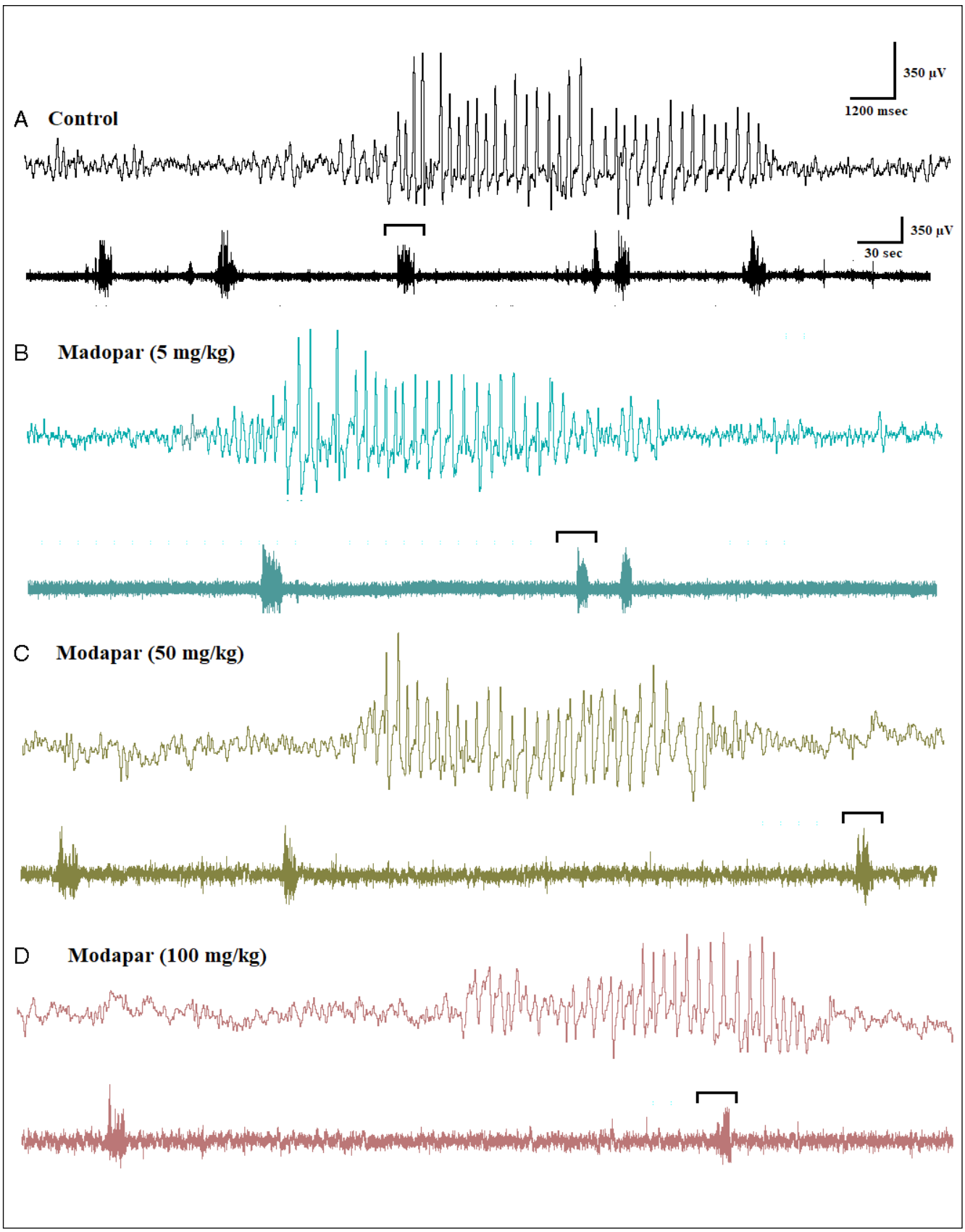

Fig. 1. Typical SWDs were recorded in 6-months-old WAG/Rij rats. ECoG recording samples for all groups.

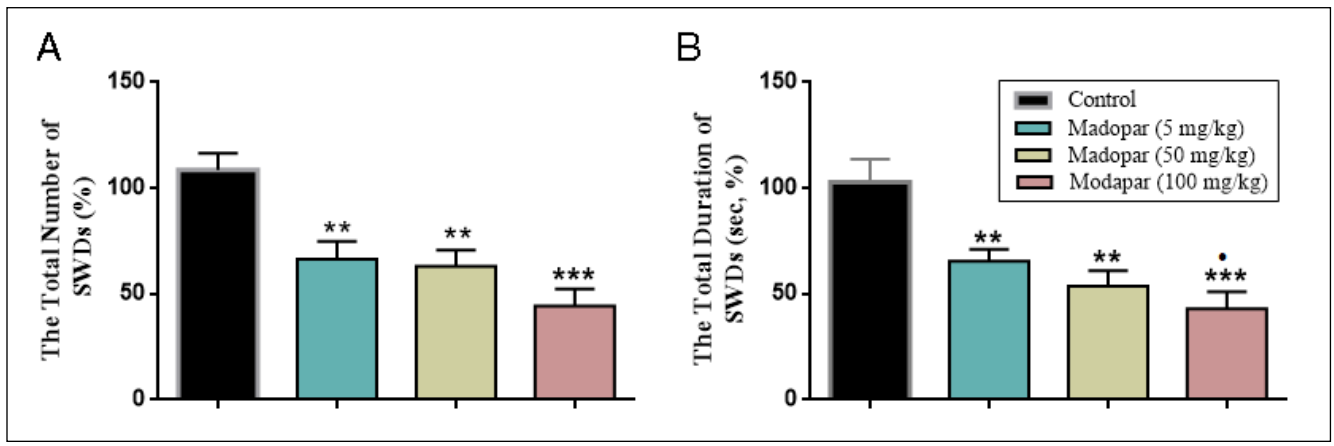

Fig. 2. The effect of Madopar (5, 50 and 100 mg/kg/i.p.) on SWDs. In all Madopar groups (5, 50 and 100 mg/kg) there was a significant reduction in the number and duration of SWDs when compared to the control group (**P<0.01; **P<0.01; ***P<0.001 respectively). The highest doses of Madopar (100 mg/kg) significantly reduced the duration of SWDs when compared to the Madopar (5 mg/kg) group (•P<0.05).

Table 1. The effects of intraperitoneal injection of Madopar in different doses on the number of SWD for three hours in WAG/Rij rats (Results are the Mean±SEM for all group. **P<0.01; ***P<0.001, All Madopar (5, 50; 100 mg/kg) group when compared to the control group).

The number of SWD	Saline	Madopar (5 mg/kg)	Madopar (50 mg/kg)	Madopar (100 mg/kg)
Basal	92.43±7.63	89.43±8.69	102.0±11.21	85.78±6.02
After injection	100.4±7.31	59.43±7.52**	63.06±7.64**	38.00±6.84***

Table 2. The effects of intraperitoneal injection of Madopar in different doses on the duration of SWD for three hours in WAG/Rij rats (Results are the Mean±SEM for all group. **P<0.01; ***P<0.001, All Madopar (5, 50, 100 mg/kg) group when compared to the control group; •P<0.05 Madopar (100 mg/kg) group when compared Madopar (5 mg/kg) group.

The duration of SWD	Saline	Madopar (5 mg/kg)	Madopar (50 mg/kg)	Madopar (100 mg/kg)
Basal	503.9±42.4	490.8±61.97	565.6±71.79	523.2±47.14
After injection	518.0±4.98	321.9±26.60**	303.3±41.67**	225.6±41.89***,•

Bouilleret et al. (2005) proposed that the dopamine neurotransmission system is involved in seizure control, and there is a decrease of the striatal cell uptake of dopamine in some refractory epileptic patients. The administration of apomorphine (0.5 mg/kg, i.p.) (D2 receptors agonist) suppressed the SWD for 30 min (Midzianovskaia, 1999), whereas the anti-dopamine medicines can worsen the absence seizures (Al-Tajir and Starr, 1991), as the administration of haloperidol (D2 receptor antagonist/diminishes nigrostriatal dopaminergic transmission) led to increasing the SWD (Midzianovskaia, 1998). In the present study, the administration of Madopar reduced the total number and duration of SWDs, and the greatest effect was seen at 100 mg/kg dose, which even significantly reduced the duration of SWDs when compared to 5 mg/kg Madopar.

The changes of dopamine signaling pathways were not detected in WAG/Rij rats at the age of 36 days, and the animals did not exhibit absence epilepsy nor behavioral symptoms of depression, despite the depression behavior in WAG/Rij rat is dopamine-dependent (Sarkisova et al., 2008). However, it was detected at the age of 3 months (Sarkisova et al., 2014), suggesting that the brain's neurochemical changes are increasing with age, and the electrical activity of absence epilepsy is displayed after the alteration in the mesolimbic dopaminergic system (when WAG/Rij rats reach 3 months

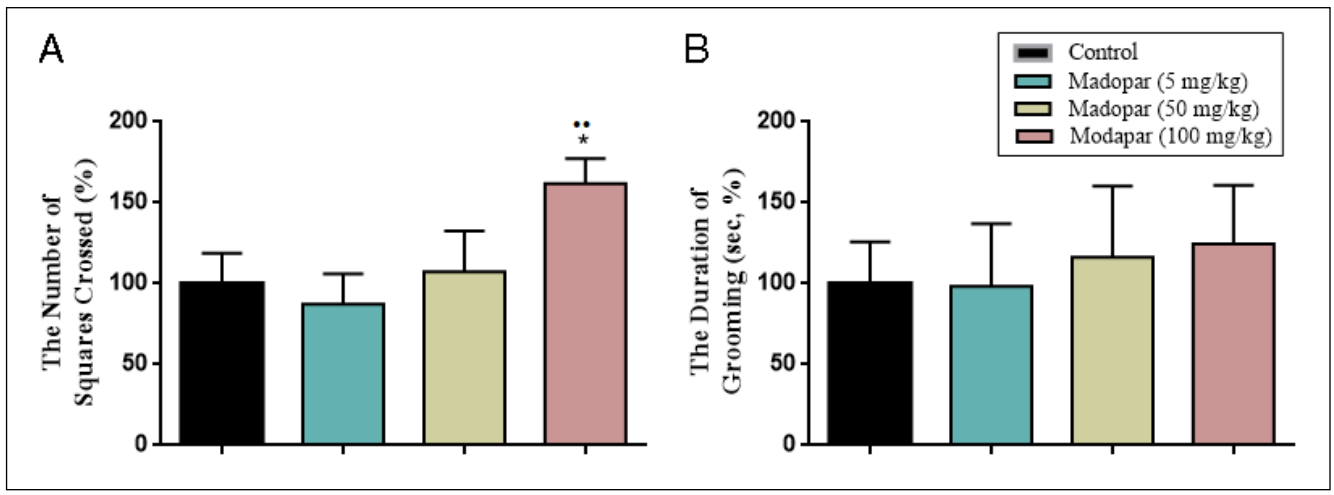

Fig. 3. The effect of Madopar (5, 50, and 100 mg/kg/i.p.) on open field test parameters. All Madopar groups (5, 50 and 100 mg/kg) did not alter the duration of grooming when compared to the control group. While the highest doses of Madopar (100 mg/kg) significantly increased the number of squares crossed in the open field test when compared to the control and Madopar (5 mg/kg) group. Statistically significant differences from the control group and Madopar groups were denoted by (*P<0.05). Statistically significant differences from the Madopar (5 mg/kg) and Madopar (100 mg/kg) groups were denoted by ••P<0.01.

Table 3. The effects of intraperitoneal injection of Madopar in different doses on the open field test for five min in WAG/Rij rats (Results are the Mean ± SEM for all group. *P<0.05. All Madopar (25, 50, 100 mg/kg) group when compared control group; ••P<0.01 Madopar (100 mg/kg) group when compared Madopar (5 mg/kg) group).

Open field test	Control Saline	Madopar (5 mg/kg)	Madopar (50 mg/kg)	Madopar (100 mg/kg)
The Number of The Squares Crossed	48.67±9.14	42.33±9.00	52.00±12.19	78.33±7.52*,••
The Duration of Grooming	11.33±3.42	11.83±4.66	14.00±5.30	15.01±4.37

old). The results of the administration of Madopar in the present study corroborate the involvement of the dopaminergic system in the cessation of SWD in absence epilepsy.

Functional magnetic resonance imaging (fMRI) revealed that there are subcortical structures involved in the interictal discharges including the basal ganglia (Federico et al., 2005), and a striatal deactivation accompanied the thalamocortical activation that indicates a striatal contribution to end the epileptic discharge (Moeller et al., 2008). The dopamine in the nigro-striatal pathway is a key controller for the basal ganglia-thalamo-cortical circuits, and this supports the antiepileptic effect of dopamine (Rektor et al., 2012). Moreover, an autoradiography study revealed that there is a reduction in the density of D1 receptors accompanied by an increment of D2 receptor density in WAG/Rij rats (which exhibit the absence seizure activity) (Birioukova et al., 2005). The increment in the density of the D2 receptor is an adaptive mechanism that comes after the demise of dopamine neurons and deficiency of neurotransmitters (Starr, 1996). It indicates that the Madopar reduced the activity of the epileptic discharge *via* such receptors, as we observed the reduction of SWD number and duration after the administration of Madopar.

In the open field test, less squares crossed are interpreted as a sign of increased anxiety, and *vice versa*. The WAG/Rij rat is considered an excellent absence epilepsy model with depression-like behavior. The dopaminergic anomaly is a major factor that provokes depression-like behavior in this model (Sarkisova et al., 2014; Sarkisova and van Luijtelaar, 2011). The results obtained from the open field test showed that there is an increase in the squares crossed after the administration of Madopar at a dose of 100 mg/kg, but not with the 5 nor 50 mg/kg doses. This can be clarified by two hypotheses. First, the high dose only would be enough to activate the miserly number of D1 receptors and exert its positive locomotor effect. Second, the

100 mg/kg dose has the greatest effect on decreasing the number of SWDs, so this decrement in the absence of epileptic activity was accompanied by the decrease of the depression-like behavior. In Parkinson and Huntington diseases, the start of motor impairments is generally preceded by depressed symptoms, implying that symptoms of depression can be triggered by even minor changes in the dopaminergic system and aren't just a psychological reaction to growing motor deficits (Sarkisova and van Luijtelaar, 2011), and this may support the first hypothesis.

Amabeoku and Chikuni (1993) showed that L-dopa shortened the onset of chloroquine-induced seizures, but benserazide did not affect the seizures induced by chloroquine. However, the seizure-inducing action of L-dopa was greatly enhanced by benserazide. Chouinard et al. (1977) concluded that benserazide did not alter the anxiety and depressive mood in schizophrenia patients. L-dopa is a dopamine precursor that has the ability to cross the blood-brain barrier (BBB) and enter brain tissue (Cedarbaum 1985). Benserazide, which is a peripheral dopa decarboxylase enzyme inhibitor, cannot cross the blood-brain barrier and is responsible for enhancing L-dopa levels in the brain (Hagan et al., 1980; Tillage et al., 2021). According to these studies, benserazide alone does not affect seizure and anxiety-like behaviors. As Madopar consists of L-dopa and benserazide, benserazide may have reduced anxiety-like behaviors and absence seizures in WAG/Rij rats with absence epilepsy by increasing the efficacy of L-dopa.

CONCLUSION

The present study revealed that the highest Madopar dose (100 mg/kg) had the greatest reducing effect on the number and duration of SWDs, and it also increased the number of squares crossed in the open field test when compared to the control and 5 mg/kg Madopar groups. In conclusion, Madopar reduced the absence-like seizure and the anxiety-related behavior.

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