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Coenzyme Q10 increases absence seizures in WAG/Rij rats: The role of the nitric oxide pathway

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ABSTRACT

Several results have suggested that coenzyme Q10 has protective effects in different models of epilepsy. This study was designed to investigate the acute effect of coenzyme Q10 in genetic absence epileptic WAG/Rij rats. We also determined the role of L-arginine (L-Arg), a biological precursor of nitric oxide (NO), and 7-nitroindazole (7-NI), an inhibitor of neuronal NO synthase (nNOS), on the effects of coenzyme Q10. Electrocorticography (ECoG) recordings were obtained during the 180 min after the administration of the different doses of coenzyme Q10 (25, 50, 100 and 200 mg/kg), L-Arg (500 and 1000 mg/kg), 7-NI (25 and 50 mg/kg) or the combinations of coenzyme Q10 (100 mg/kg) with L-Arg (1000 mg/kg) or 7-NI (50 mg/kg). The total number of spike wave discharges (SWDs) and the mean duration of SWDs were calculated and compared. Coenzyme Q10, at the doses of 50 mg/kg, increased the total number of SWDs but did not changed the mean duration of SWDs. Coenzyme Q10 (100 and 200 mg/kg) or L-Arg (500 and 1000 mg/kg) increased both the total number and the mean duration of SWDs. In contrast, the administration of 7-NI (25 and 50 mg/kg) decreased the total number of SWDs and the mean duration of SWDs. Coadministration of L-Arg enhanced the effect of coenzyme Q10 on the total number of SWDs but not on the mean duration of SWDs. Moreover, the coadministration of 7-NI abolished the effect of coenzyme Q10 on both SWD parameters. The electrophysiological evidences from this study suggest that administration of coenzyme Q10 increases absence seizures by stimulating the synthesis of neuronal NO.

1. Introduction

Absence epilepsy is a typical example of idiopathic generalized epilepsy. Absence epilepsy occurs in the form of loss of consciousness and freezing, showing SWDs at 3–4 Hz frequency in electroencephalogram (EEG), and it is a type of nonconvulsive and idiopathic epilepsy that lasts for 10–30 s (Annegers, 2001; Grosso et al., 2005). It is known that the thalamocortical loop and, in particular, the ventrobasal (VB) core of the thalamus and the thalamic reticular nucleus (TRN) have an important task in the emergence of typical SWDs (Avoli and Gloor, 1982; Blumenfeld, 2005).

Animal models of seizures have played a primary role in understanding the main mechanisms of epileptogenesis and the development of novel antiepileptic drugs (Sarkisian, 2002; Aygun et al., 2015). Although there are different chemically induced absence epileptic seizure models, the use of genetic models is more highly favored for studying absence epilepsy. Wistar albino Glaxo-Rijswijk (WAG/Rij) rats, which are genetically engineered animals with spontaneous spike discharges, are used in the studies of absence epilepsy (Coenen and Van Luijtelaar, 2003). Pharmacological, morphological and electrophysiological features of absence seizures in these rats are similar to those seen in human patients (Depaulis and Van Luijtelaar, 2006).

Coenzyme Q10, one of the most studied antioxidants in recent years, is an important component of the mitochondrial electron transport system. Coenzyme Q10 exists mainly in the mitochondria membrane and plays a key role in energy production (Crane, 2001; Singh et al., 2002). Many studies have suggested that the administration of coenzyme Q10 has protective effects in neurodegenerative diseases, such as Alzheimer's, Parkinson's, Huntington's and amyotrophic lateral sclerosis, due to its reducing effects on oxidative stress (Spindler et al., 2009; Mecocci and Polidori, 2012; Seet et al., 2014; Kasparova et al., 2006; Kawasaki et al., 2012; Somayajulu et al., 2005). There are a limited number of studies investigating the role of coenzyme Q10 administration on epilepsy. Administration of coenzyme Q10 for two weeks decreased the number and severity of seizures in the pilocarpine-induced temporal lobe epilepsy model (Tawfik, 2011). Sattarinezhad et al. (2014) demonstrated that subchronic (7 days), but not acute, oral application of coenzyme Q10 increased the latency time and threshold

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to seizures in pentylenetetrazole-induced seizures, and decreased the incidence of tonic seizures in electroshock-induced seizures. Moreover, the anticonvulsant effect of subchronic treatment of coenzyme Q10 was found to be potentiated by L-Arg and reduced by L-NAME in pentylenetetrazole-induced seizures (Sattarinezhad et al., 2014). These results suggest a relationship between coenzyme Q10 and the NO pathway.

No evidence is available for the effect of coenzyme Q10 in absence seizures. The aim of this study was to investigate the role of coenzyme Q10 on the SWD parameters in WAG/Rij rats. Additionally, the role of the NO pathway on the effect of coenzyme Q10 was also examined.

2. Materials and methods

2.1. Animals

After obtaining local ethics committee approval (2016/65), specific-pathogen-free absence epileptic inbred male WAG/Rij rats weighing 213 ± 12 g were purchased from the Animal House of Cumhuriyet University. All animals were housed in a temperature controlled (23 ± 1 °C) environment on a 12 h light/dark cycle with free access to standard rat food and tap water. All experiments were conducted in accordance with the ARRIVE guidelines and the Guide for the Care and Use of Laboratory Animals as per the US National Institutes of Health (NIH Publications No. 8023, revised 1978).

2.2. Placement of electrodes

Animals were anesthetized and sedated with ketamine/xylazine (90/10 mg/kg, i.p.) and they were placed on the stereotaxic device. The skin was removed by an incision, approximately 3 cm in the rostrocaudal direction, and subcutaneous tissue was removed. After determining the reference point (bregma) three holes were drilled without damaging the dura and three screws were placed in these holes as coordinates: first electrode, 4 mm anterior and 3 mm right lateral to bregma (frontal cortex); second electrode, 4 mm posterior and 3 mm right lateral to bregma (occipital cortex); and reference electrode, 4 mm posterior and 3 mm left lateral to bregma (Arslan et al., 2017). Bipolar stainless steel electrodes (Plastics One, Roanoke, Virginia, USA) were wrapped around the screws, and the electrodes were fixed to the skull with dental acrylic cement. Buprenorphine hydrochloride (0.1 mg/kg) was injected intramuscularly for analgesia after surgery.

2.3. Electrocorticography (ECoG) recordings

After a 7 day healing period, animals were individually placed in glass cages (40 × 40 x 40 cm) and were connected to the recording system with a conductor cable for 180 min for habituation. The electrocorticography (ECoG) recordings were obtained during the 180 min before and after the intraperitoneal administration of the different doses of coenzyme Q10 (25, 50, 100 and 200 mg/kg), L-Arg (500 and 1000 mg/kg), 7-NI (25 and 50 mg/kg) or the combinations of coenzyme Q10 (100 mg/kg) with L-Arg (1000 mg/kg) or 7-NI (50 mg/kg). Each group was composed of at least six rats. The ECoG activities were monitored on a four-channel data acquisition unit (Labchart 7-Pro, PowerLab, 4/SP, AD Instruments, Castle Hill, Australia) and analyzed off-line. All rats showed SWDs characterized by paroxysmal unresponsiveness to environmental stimuli.

2.4. Drugs

Coenzyme Q10, L-Arg and 7-NI were purchased from Sigma-Aldrich. The doses of coenzyme Q10 and 7-NI were dissolved in soybean oil and the doses of L-arg were dissolved in sterile physiological saline in a volume of 1.5 ml, 0.5 ml and 0.5 ml, respectively. The doses of L-Arg and 7-NI were determined in accordance with previous studies (Smith et al., 1996; Kaputlu and Uzbay, 1997; Bosnak et al., 2007; Aslan et al., 2010).

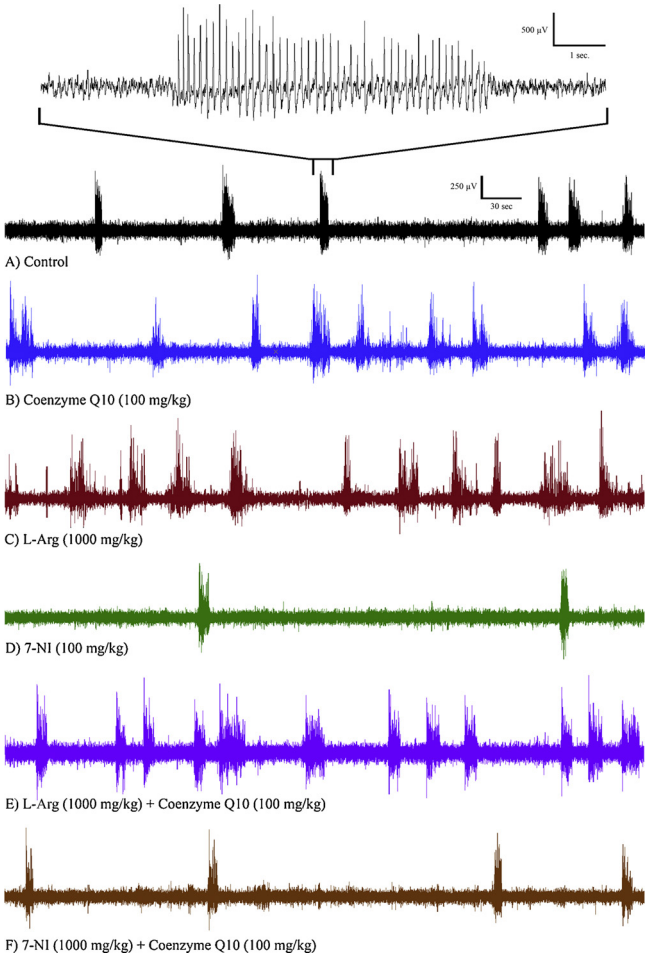

Fig. 1. Representative ECoG recordings of SWDs at 90 min after drug administration. Control rats were treated with soybean oil.

2.5. Electrocorticographical and statistical analysis

The total number and the mean duration of SWDs were calculated, by using the raw data obtained from Labchart 7-Pro, with an excel program. Groups were compared using the GraphPad Instat v3.06 (GraphPad Software, San Diego, CA, USA). The Kolmogorov-Smirnov test was used to determine the normal distribution of the data. After verifying that the data were normally distributed, one-way analysis of variance (ANOVA) and Tukey-Kramer post hoc tests were performed for multiple comparisons among after injection values. For the control group, calculated data before and after soybean oil administration were compared with the paired-sample t-test. For all statistical tests, $p < 0.05$ was considered statistically significant.

3. Results

Representative SWDs recordings obtained 90 min after the administration of drugs are shown in Fig. 1A–F. The number of SWDs in basal activity ranged from 86 to 113, and the duration of SWDs was ranged from 4.54 to 6.12 s. There was no difference in the SWD parameters during the basal activity between the groups (data not shown). In the control group, the total number (100.6 ± 4.4) and the mean duration (5.45 ± 0.12 s) of SWDs during basal activity was not changed after the injection of soybean oil (the total number of SWDs: 99.3 ± 4.6, the mean duration of SWDs: 5.46 ± 0.14 s) (data not shown).

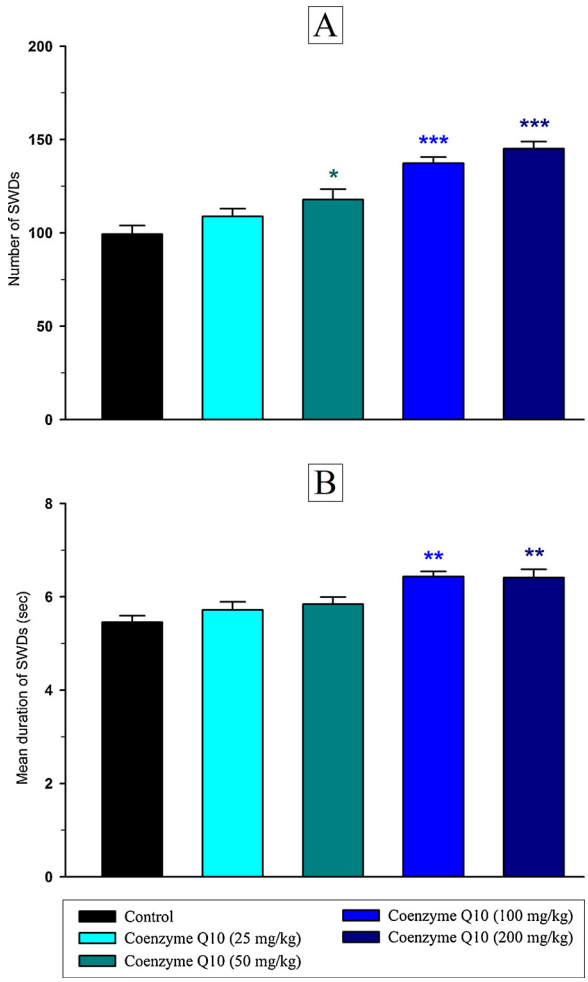

Fig. 2. (A) Intraperitoneal administration of coenzyme Q10, at the doses of 50, 100 and 200 mg/kg, increased the total number of SWDs (B) Coenzyme Q10, at the doses of 100 and 200 mg/kg, increased the mean duration of SWDs. *p < 0.05, **p < 0.01, ***p < 0.001 indicate significant differences compared to control group.

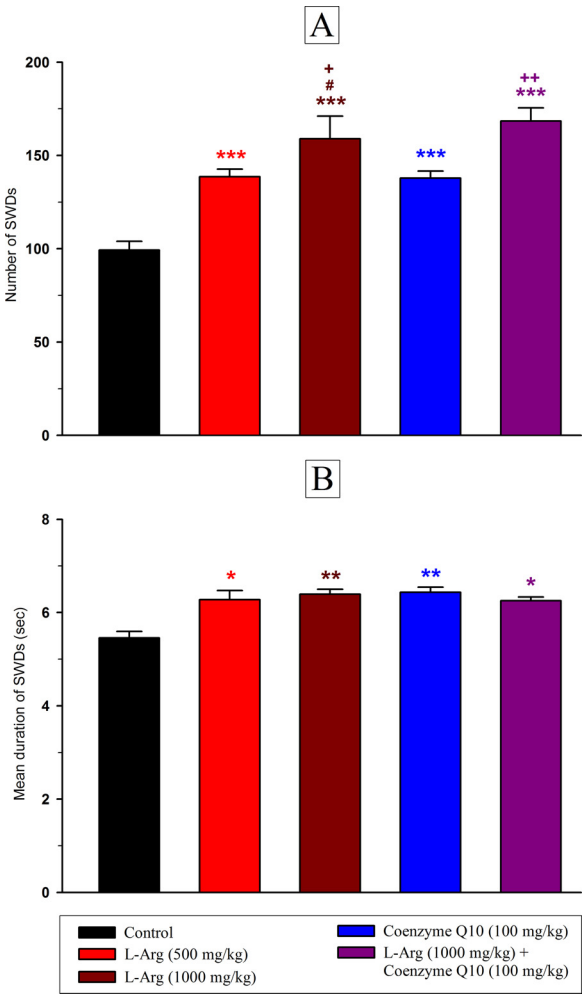

Fig. 3. (A) Intraperitoneal administration of 500 and 1000 mg/kg L-Arg increased the total number of SWDs compared to the control group. The dose of 1000 mg/kg L-Arg was significantly higher than 500 mg/kg L-Arg or 100 mg/kg coenzyme Q10. Coadministration of L-Arg (1000 mg/kg) with coenzyme Q10 increased the total number of SWDs compared to coenzyme Q10. (B) L-Arg (500 and 1000 mg/kg) or the coadministration of L-Arg (1000 mg/kg) with coenzyme Q10 significantly increased the mean duration of SWDs compared to the control group. *p < 0.05, **p < 0.01, ***p < 0.001 indicate significant differences compared to control group. +p < 0.05, ++p < 0.01, indicate significant differences compared to coenzyme Q10 (100 mg/kg) group. #p < 0.05 indicate a significant difference compared to 500 mg/kg L-Arg group.

3.1. Effects of different doses of coenzyme Q10 on the SWD parameters

The administration of 25 mg/kg coenzyme Q10 did not affect the total number or the mean duration of SWDs compared to the control group. The total number of SWDs was found to be increased at the doses of 50, 100 and 200 mg/kg of coenzyme Q10 compared to the control group ($p < 0.05$; $p < 0.001$; $p < 0.001$, respectively) (Fig. 2A). Similarly, the mean duration of SWDs was increased after injection of 100 and 200 mg/kg of coenzyme Q10 compared to the control group ($p < 0.01$; $p < 0.01$, respectively) (Fig. 2B). The 100 mg/kg dose of coenzyme Q10 was chosen for the combination groups as no significant difference was detected between the groups of 100 and 200 mg/kg. The total number of SWDs was 137.3 ± 3.3 (Fig. 2A) and the mean duration of SWDs was 6.43 ± 0.11 s after the injection of 100 mg/kg coenzyme Q10 (Fig. 2B).

3.2. Effects of L-Arg and L-Arg + coenzyme Q10 combination on the SWD parameters

L-Arg, at the doses of 500 and 1000 mg/kg, increased the total number ($p < 0.001$; $p < 0.001$, respectively) and the mean duration ($p < 0.05$; $p < 0.01$, respectively) of SWDs compared to the control group (Fig. 3A and B). The dose of 1000 mg/kg L-Arg was chosen for the combination group, as this dose was significantly more effective than 500 mg/kg ($p < 0.05$) (Fig. 3A). After the injection of 1000 mg/kg L-Arg, the total number of SWDs was 159.0 ± 12.1, and the mean duration of SWDs was 6.39 ± 0.10 s (Fig. 3A and B). The total number of SWDs after the administration of L-Arg (1000 mg/kg) was found to be higher compared to that of coenzyme Q10 (100 mg/kg) ($p < 0.05$) (Fig. 3A).

The coadministration of L-Arg (1000 mg/kg) with coenzyme Q10 (100 mg/kg) increased the total number of SWDs when compared to coenzyme Q10 (100 mg/kg) ($p < 0.05$), but there was no significant difference compared to L-Arg (1000 mg/kg) (Fig. 3A). The mean duration of SWDs after the coadministration of L-Arg (1000 mg/kg) with coenzyme Q10 (100 mg/kg) was not found to be different when compared to that of coenzyme Q10 (100 mg/kg) or L-Arg (1000 mg/kg) (Fig. 3B). The total number of SWDs was 168.5 ± 7.0, and the mean duration of SWDs was 6.26 ± 0.08 s after injection of L-Arg with coenzyme Q10 (Fig. 3A and 3B).

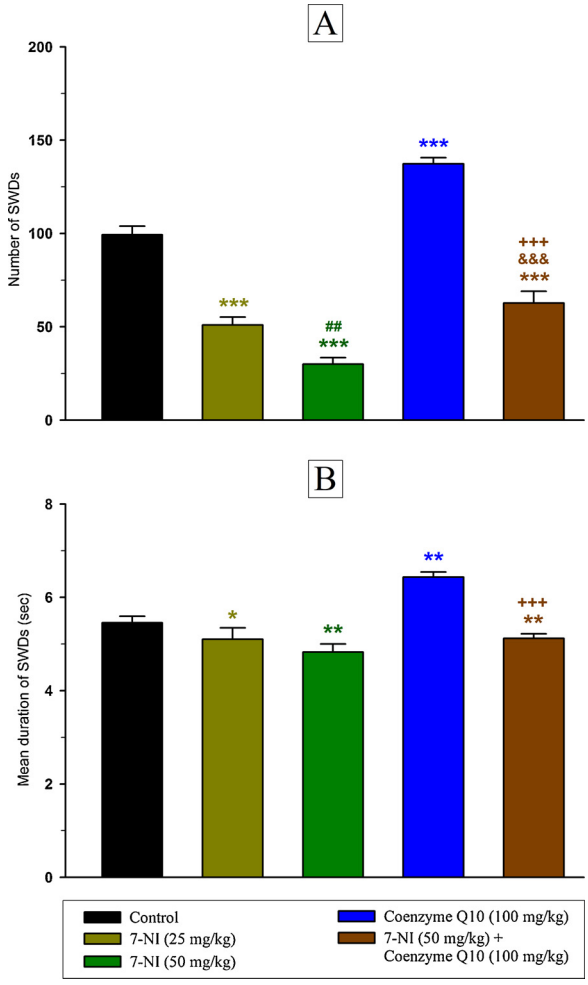

Fig. 4. (A) Intraperitoneal administration of 25 and 50 mg/kg 7-NI decreased the total number of SWDs compared to the control group. Coadministration of 7-NI (50 mg/kg) with coenzyme Q10 significantly decreased the total number of SWDs compared to the control or coenzyme Q10 groups. (B) 7-NI, at the doses of 25 and 50 mg/kg, decreased the mean duration of SWDs compared to the control group. Coadministration of 7-NI (50 mg/kg) with coenzyme Q10 significantly decreased the mean duration of SWDs compared to the control or coenzyme Q10 groups. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ indicate significant differences compared to control group. +++$p < 0.001$ indicate a significant difference compared to coenzyme Q10 (100 mg/kg) group. ##$p < 0.01$ indicate a significant difference compared to 25 mg/kg 7-NI group. &&&$p < 0.001$ indicate a significant difference compared to 50 mg/kg 7-NI group.

3.3. Effects of 7-NI and 7-NI + coenzyme Q10 combination on the SWD parameters

7-NI, at the doses of 25 and 50 mg/kg, decreased the total number ($p < 0.001$; $p < 0.001$, respectively) and the mean duration ($p < 0.05$; $p < 0.01$, respectively) of SWDs compared to control group. The dose of 50 mg/kg 7-NI was chosen for the combination group as this dose was significantly more effective than the low dose of 7-NI ($p < 0.05$) (Fig. 4A). The total number of SWDs was 30.0 ± 3.4, and the mean duration of SWDs was 4.83 ± 0.18 s after the administration of 7-NI (50 mg/kg) (Fig. 4A and B).

The coadministration of 7-NI (50 mg/kg) with coenzyme Q10 (100 mg/kg) decreased the total number ($p < 0.001$) and the mean duration ($p < 0.001$) of SWDs compared to coenzyme Q10 (100 mg/kg), and increased only the total number of SWDs ($p < 0.001$) compared to 7-NI (50 mg/kg) (Fig. 4A and 4B). The total number of SWDs was 62.7 ± 6.4, and the mean duration of SWDs was 5.12 ± 0.10 s, after the coadministration of 7-NI with coenzyme Q10 (Fig. 4A and B).

4. Discussion

Coenzyme Q10, an important component of the mitochondrial electron transport system, plays a key role in energy production (Crane, 2001; Singh et al., 2002). It is suggested that exogenous administration of coenzyme Q10 has neuroprotective properties in neurodegenerative diseases (Spindler et al., 2009; Mecocci and Polidori, 2012; Seet et al., 2014; Kasparova et al., 2006; Kawasaki et al., 2012; Somayajulu et al., 2005). However, there are only several experimental studies on the role of coenzyme Q10 in epilepsy. The intraperitoneal administration of coenzyme Q10 for two weeks reduced the number and severity of seizures and reduced oxidative stress in the pilocarpine-induced temporal lobe epilepsy model (Tawfik, 2011). Acute oral administration of coenzyme Q10 (at the doses of 400 mg/kg and below) was not effective in pentylenetetrazole-induced seizures (Sattarinezhad et al., 2014). However, subchronic oral doses of coenzyme Q10 (50 mg/kg or more) have been shown to have anticonvulsant effects in pentylenetetrazole- and electroshock-induced seizure models (Sattarinezhad et al., 2014). In the present study, acute intraperitoneal administration of coenzyme Q10, at the doses of 50, 100 and 200 mg/kg, increased the total number of SWDs, and the mean duration of seizures, except for the dose 50 mg/kg. Our results suggest that coenzyme Q10 has proconvulsant effects on absence seizures, in contrast to the anticonvulsant effects of the status epilepticus and generalized seizure models.

NO is involved in important physiological processes in diseases of the central nervous system, such as epilepsy (Guix et al., 2005). The administration of the NO precursor L-Arg showed anticonvulsant activity in penicillin-induced epileptiform activity (Bosnak et al., 2007; Aslan et al., 2010) and PTZ induced seizures (Kaputlu and Uzbay, 1997). However, in a study of absence epilepsy, Przewlocka et al. (1996) demonstrated that the NO donors S-nitroso-*N*-acetylpenicillamine (SNAP), 3-morpholino-sydnonimine (SIN-1) or sodium nitroprusside (SNP) increased the number of SWDs in WAG/Rij rats. In accordance with this study, our data indicated that intraperitoneal administration of L-Arg increased the SWD parameters in WAG/Rij rats. In line with this result, intraperitoneal administration of 7-NI decreased the absence seizures in WAG/Rij rats. Thus, our results, together with the results of the aforementioned study, strongly suggest the NO pathway has a role in absence seizures, at least in WAG/Rij rats.

Although the cellular mechanisms underlying absence seizures are not fully understood, increased GABAergic transmission remains one of the main accepted hypotheses (Wong, 2010). To our knowledge, oscillatory burst-firing of absence seizures originate from the thalamocortical circuit that contains the thalamic reticular nucleus, thalamic relay neurons and neocortical pyramidal cells. This pathway plays a role in the formation of sleep spindles and spike wave discharges (Futatsugi and Riviello, 1998). It was reported that hyperpolarization by inhibitory neurotransmitters, such as GABA, activate low voltage-activated T-type calcium channels; then, rapid and transient calcium influx creates low-threshold calcium potentials, which can generate the firing of sodium and potassium channel-mediated action potentials (Jahnsen and Llinas, 1984; Cain and Snutch, 2013). In this study, we did not examine the mechanisms of L-Arg induced increase or the 7-NI induced decrease in the SWD parameters. There is serious evidence indicating the release of GABA, a main inhibitory neurotransmitter in the brain, with NO (Bains and Ferguson, 1997) or different NO donors (Kuriyama and Ohkuma, 1995; Seilicovich et al., 1995; Ohkuma et al., 1995; Paul and Jayakumar, 2000). Paul and Jayakumar (2000) reported that the intraperitoneal administration of L-Arg (1000 mg/kg), the same dose as ours, increased GABA levels by inhibiting GABA transaminase activity in the brain. Therefore, we suggest that L-Arg causes an increase and 7-NI causes a decrease in absence seizures by increasing and decreasing GABA release, respectively.

Several studies have suggested that exogenous administration of

coenzyme Q10 increased the production of NO. Durán-Prado et al. (2014) reported that coenzyme Q10 application prevented the reduction of NO in human umbilical vein endothelial cells. In an vitro study, coenzyme Q10 resulted in an inhibitory effect on the growth of colon cancer HCT116 cells via NO production (Jang et al., 2017). Kozaeva et al. (2017) suggested that coenzyme Q10 increased NO-mediated vasodilation in rat aorta similarly to L-Arg. In addition to these studies, related to the interaction of coenzyme Q10 with the other forms of NOS, oral administration of coenzyme Q10 for 4 weeks activated the Akt-nNOS cascade and increased NO production via nNOS phosphorylation in the nucleus tractus solitarius (Chen et al., 2019). In our study, coenzyme Q10 induced increase in the total number and mean duration of SWDs was found to be enhanced with the administration of L-Arg and decreased with the administration of 7-NI. With the results of others, we suggest that coenzyme Q10 has a proconvulsant effect in absence seizures by causing NO release via the activation of nNOS. Similar to our opinion, Sattarinezhad et al. (2014) suggested a possible role of NO in the antiseizure activity of coenzyme Q10. However, the doses of L-Arg and 7-NI coadministered with coenzyme Q10 in our study were high, and each affected the SWD parameters alone. Thus, further studies examining the effect of low doses of L-Arg and 7-NI alone and in combination with coenzyme Q10 are needed to support our hypothesis.

5. Conclusions

Our study showed that intraperitoneal acute administration of coenzyme Q10 dose-dependently increased seizures in genetic absence epileptic WAG/Rij rats. While the NO precursor L-Arg increased the total number and mean duration of SWDs, the nNOS inhibitor 7-NI decreased these SWD parameters. Coadministration of L-Arg increased, and 7-NI decreased, the effect of coenzyme Q10. Our results suggest that exogenously administered coenzyme Q10 causes a proconvulsant activity in absence seizures through stimulating the NO pathway. Consequently, patients with absence epilepsy should carefully use coenzyme Q10 as a food supplement.

Conflict of interest

The authors declare no conflict of interest.

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