



Positive effect of moderate-intensity aerobic activity on pentylenetetrazol-induced epileptic behaviors in pregnant mice and cognitive performance in adult male offspring

Ayoob Sabaghi¹ · Ali Heyrani¹ · Amir Kiani² · Namdar Yousofvand³

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Abstract

Purpose Epilepsy is one of the common neurological disorders. It has been reported that physical activity can be a complementary therapy to treat seizures. Therefore, the present study was designed to investigate the effect of aerobic training on pentylenetetrazol (PTZ)-induced seizure in pregnant mice.

Methods The kindled female mice were divided into eight groups including (1) pregnant mice (PC) treated with PTZ without physical training (PT), (2) PC treated with PTZ with aerobic training (AT), (3) PC treated with normal saline (NS), (4) PC without any injection in pregnancy, (5) non-PC treated with PTZ without PT, (6) non-PC treated with PTZ with AT, (7) non-PC treated with NS and (8) non-PC without any injection. The seizure activity was measured for half an hour after PTZ injection and anxiety activity was assessed 2 h after PTZ injection. Also, at postnatal day 94, cognitive performance at male offspring of the groups was evaluated.

Results The results showed that aerobic training reduced seizure severity and restored seizure-induced anxiety in pregnant and non-pregnant mice to control levels. It was also observed that aerobic activity during pregnancy would restore the cognitive function of the offspring in pregnant mice treated with PTZ to the male offspring's level in control group.

Conclusion Generally, the results of this study showed that moderate-intensity AT is an appropriate treatment strategy for reducing the severity of seizure, seizure-induced anxiety and also prevents cognitive impairment due to seizure induction during pregnancy in the male offspring.

Keywords Seizure · Pregnancy · Aerobic training · Anxiety · Cognitive performance · Offspring

Introduction

Epilepsy is a chronic disease that causes frequent seizures and its reason is abnormal electrical discharge in neuronal brain cells [1]. Prevalence of epilepsy: In advanced countries, 4–7 out of 1000 people suffer from this disease [2]. The infants of the mothers with epilepsy are exposed to a variety of adverse pregnancy outcomes. The generalized

tonic–clonic seizures not only can lead to increased apoptotic proteins in the hippocampus and cognitive problems in the offspring [3, 4], but also to seizure-induced hypoxia. So this phenomena causes several pathological effects such as ontogeny and neurobehavioral in fetus and infant brain, respectively [5, 6].

Antiepileptic drugs have been able to control seizure attacks but they are several adverse effects in mother's, fetus and newborns. This effects including reduced cognitive function [7], liver failure, [8] in mothers, neural tube defect, congenital heart disease, urinary malformations, and cleft palate in the fetus [9, 10] and reduced intelligence quotient in the newborns [11]. It seems that physical activities can be able reduce the number or severity of seizure and decrease outcome from this drugs. Human studies have generally shown that regular physical exercise can decrease seizure frequency in patient [12, 13]. Animal studies have been carried out to elucidate the mechanisms by which aerobic

✉ Ali Heyrani
iliaheirani2004@gmail.com

¹ Department of Physical Education and Sport Sciences, Razi University, Kermanshah, Iran

² Pharmaceutical Sciences Research Center, School of Pharmacy, Kermanshah University of Medical Sciences, Kermanshah, Iran

³ Department of Biology, Razi University, Kermanshah, Iran

training can lead to positive effects in epilepsy. So, physical exercise reduces the development of amygdala kindling [14]; the frequency of seizures induced by pilocarpine [15]; decreases CA1 hyper-responsiveness [16] and plasticity changes in the hippocampal formation in rats with epilepsy [17].

However, there is no consistent information about the magnitude of these effects in female as most studies have addressed the effects of physical activity on epilepsy in male mice models; but the female population is also worthy of attention. Therefore, it is necessary to investigate the effect of aerobic training in females especially in pregnant ones due to the effects they can have on fetuses and infants. In this study, it is attempted to determine whether aerobic physical activity during pregnancy can interfere with seizure severity induced by pentylenetetrazol (PTZ) in pregnant mice. In addition, we assessed effect of seizure and aerobic training in pregnancy on cognitive performance of adult male offspring in pregnant mice treated with PTZ.

Methods

Subjects and general housing conditions

Eight-week-old male and female ICR mice are purchased from the Animal Center Laboratory of Kermanshah, Iran University of Medical Sciences, Iran. The animals are kept in a standard polycarbonate cage in a room with a controlled temperature (23 ± 1 °C) with a fixed 12-h light–dark cycle (08:00–20:00) and free access to water and food. These conditions are considered as the appropriate conditions at all stages of the laboratory.

The kindling procedure

The female mice received thirteen intraperitoneal (i.p.) injections [18] of 40 mg/kg of PTZ (Sigma-Aldrich, Germany) and kindled every 48 h [19] and in 11th, 12th and 13th injections they were monitored 30 min after injection and seizures were classified according to the modified Racine scale as described by Becker et al.: no response—stage 0; ear and facial twitching—stage 1; myoclonic jerks without breeding—stage 2; myoclonic jerks, rearing—stage 3; turning over into side position, clonic–tonic seizures—stage 4; turning over into back position, generalized clonic–tonic seizures—stage 5 [20]. Only the animals that showed the seizure scores of stages 4 and 5 in the last three injections entered the next stage [21]. To maintain the kindling state, the animals were again challenged 10 days after the last day of the completion of kindling with i.p. injection of 40 mg/kg of PTZ drug. At this stage, only the animals that experienced

the stages 4 and 5 of the seizure score entered the pregnancy stage [19].

Familiarization of animals with treadmill

Animals were familiarized with treadmill in training groups during 3 days prior to the beginning of pregnancy for 15 min per day at a speed of 8 m/min with 0% degree incline. Electric shocks were used rarely during the running familiarization to stimulate the animals to run. Trainability of mice was measured on the basis of their performance on a scale of 1–5; scale parameters are as follows: 1—lack of running, 2—running under the average level (interrupted, stops while running, running in the opposite direction), 3—average running, 4—above the average running (regular, falling behind the treadmill) and 5—excellent running (always in front of the treadmill). Animals showing the score of 3 or higher were included in the aerobic training group [22].

Breeding

After the last training session of familiarizing with treadmill and selection of the mice, to facilitate mating, the female and male mice were kept in separate cages in one-by-one manner. Successful mating was determined on the next morning (8:00 AM) by the presence of vaginal plugs and this day was considered as gestational day (GD) 0 [23]. After specifying the pregnant mice, they were transferred from the breeding cage to the standard cage and kept separately.

Induction of seizure

The kindled female mice were divided into eight groups: (1) pregnant mice (PC) with intraperitoneal (i.p.) injection of 40 mg/kg of PTZ within the 14th–19th days of pregnancy every 48 h [19] without physical training (PT) during pregnancy (PC-PTZ-non-PE, $n = 12$); (2) PC with [18] injection of 40 mg/kg of PTZ within the 14th–19th days of pregnancy every 48 h with aerobic training (AT) during pregnancy (PC-PTZ-AT, $n = 12$); (3) PC which received the i.p. normal saline (NS) in volume equal to PTZ on GD 14–19 every 48 h (PC-NS, $n = 10$), (4) PC without injection during pregnancy (PC-Con, $n = 10$), (5) non-PC treated with PTZ without physical training (non-PC-PTZ-non-PE, $n = 12$), (6) non-PC treated with PTZ with aerobic training (non-PC-PTZ-AT, $n = 12$), (7) non-PC which received the i.p. NS in volume equal to PTZ, (PC-NS, $n = 10$), and (8) non-PC without any injection (non-PC-Con, $n = 10$). Active pregnant mice participated in aerobic trainings on the treadmill from the 1st to 20th day of pregnancy. Exercise sessions started with a 3-min warm-up at 8 m/min. Running time and speed were gradually increased from 10 min at 10 m/min during the first sessions to 30 min at 12 m/min over the following

training days [24]. Also, non-pregnant mice in similar procedure with pregnant mice participated in aerobic trainings. These types of trainings are classified as moderate exercises in various articles [25, 26].

Inactive female mice were on treadmill without any movements at the same time that the active female mice ran on treadmill. After injecting 40 mg/kg of PTZ into female mice in both physically inactive and active groups, the seizure score was measured according to Racine (1972), modified by Becker et al. (1992) as explained previously [20].

Checking the level of anxiety using the light–dark box

The rate of anxiety in female mice was measured between the 14th and 19th days of pregnancy once in 48 and 2 h after PTZ injection [27]. The light–dark box test is used to measure anxiety. This tool is made of a white–black wooden rectangular box (length 46 cm, width 27 cm, and height 30 cm) that is divided into two compartments by a partition (light and large: 27cm × 27 cm, dark and small: 18cm × 27 cm). These two compartments are connected by a small open center (7.5 cm × 7.5 cm) located at the center of the partition at the bottom of the box. The large compartment was open at the top, illuminated by a 100 W bulb located 90 cm above the apparatus. The small compartment had a removable black lid at the top. To start the test, each pregnant mouse was placed at the center of the light compartment, facing away from the door. The animal was allowed to freely explore both compartments for 5 min. Time spent in light compartment is measured. A decrease in the amount of time spent in the light compartment are indicative of anxiety-like behavior [23].

Reviewing the cognitive performance of the adult male offspring

Pups were housed with their littermates until weaning at postnatal day 21 and male pups from each litter were stored singly in a cage [4]. On the postnatal day 91, considered as adult period among mice [28], ten male adult offspring were selected (to reduce possible litter effects, a total of two male pups from any litter were used in this experiment) from each group and using novel object recognition task (NORT) at the 91–94 postnatal days the cognitive performance of the offspring was examined.

The NORT was conducted to assess the mice's ability to recognize a novel object, determined by their exploratory behavior. This task measures the ability to discriminate between novel and familiar, previously encountered objects. Familiarization of the animals with the experimental procedures occurred on the first 3 days, where the animal was individually placed in an empty open field without

any objects. The mice were habituated to the open field by allowing them to explore it without the objects for 15 min every day for 3 days prior to the test. The tests (sample phase and test phase) were performed on the 4th day. The objects were two small identical wooden cubes located in an open field, a square wooden box (40 × 40 × 45 cm). The NORT is divided into two phases: (1) the sample phase, where each animal was exposed to the object for 5 min; and (2) the test phase, where one object was replaced by a novel object and the time spent exploring the novel and the familiar objects was recorded for 5 min. The test phase takes place 1 hour after the sample phase [29]. Recognition memory was evaluated using a recognition index (RI) calculated for each mouse using the formula $(N-F/N+F) \times 100$, corresponding to the difference between the time exploring the novel and the familiar object, corrected for total time exploring both objects. Positive values indicate a good discrimination performance, while negative values or those around zero indicate poor discrimination capacity [30]. The objects were cleaned between testing with ethanol 70%.

Data analysis

SPSS 22.0 was used for all statistical analyses. The data are expressed as the mean \pm standard error of the mean (S.E.M). Average of seizure activity in the 14th, 16th and 18th of pregnancy after i.p.injection of PTZ and cognitive function of the male offspring were compared with Kruskal–Wallis test (nonparametric) followed by Dunn's test. The time spent in the light compartment was also evaluated by repeated measures of variance analysis. Also, seizure severity and anxiety rate between pregnant and non-pregnant mice were compared with Mann–Whitney *U* test (nonparametric). *P* values less than 0.05 were considered to be significant.

Results

The effect of aerobic training on the severity of PTZ-induced seizure

The results of Kruskal–Wallis test to study seizure activity showed that the effect of the group was significant ($\chi^2 = 31.094$, $p < 0.0001$; Fig. 1). Dunn's post hoc test indicated that aerobic training reduces seizure severity ($p < 0.05$).

Seizure severity between pregnant and non-pregnant mice

The results of Mann–Whitney's *U* test between pregnant and non-pregnant mice to study seizure severity were not significant ($p > 0.05$). See Table 1 for the results.

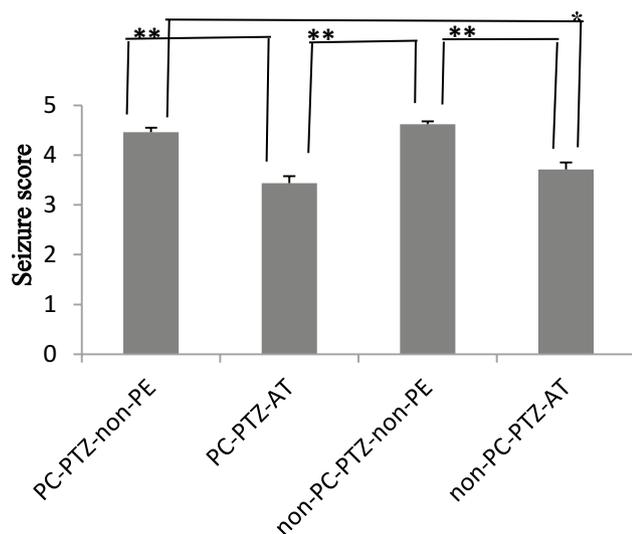


Fig. 1 Effect of aerobic exercise on PTZ-induced seizure activity. PTZ was given in a dose of 40 mg/kg (i.p.). Seizure scores were measured for 30 min after the injection of PTZ. Values are mean \pm S.E.M for each group. * $p < 0.05$ and ** $p < 0.001$ versus other group

Table 1 Seizure activity and results of Mann–Whitney’s U test

	Mean \pm SEM	Z	P
Pregnant mice	3.95 \pm 0.13	1.168	0.243
Non-pregnant mice	4.17 \pm 0.12		

The effect of aerobic training on anxiety-like behaviors

In the data analysis of the light–dark box, the results of the ANOVA test were not significant with repeated measurements in terms of the effect of time ($F_{(2,156)} = 0.514$, $p = 0.599$) and the interactive effect of group and time ($F_{(14,156)} = 1.730$, $p = 0.055$), but the effect of the group and effect of the time were significant ($F_{(1,69)} = 21.629$, $p < 0.001$; Fig. 2). Bonferroni post hoc test results showed that seizure induction in both pregnant and non-pregnant mice caused significant increase in anxiety ($p < 0.05$) and moderate-intensity aerobic training significantly inhibited seizure-induced anxiety compared to control levels ($p > 0.05$).

Anxiety rate between pregnant and non-pregnant mice

The results of Mann–Whitney’s U test between pregnant and non-pregnant mice to study anxiety were not significant ($p > 0.05$). The values for the light–dark box are presented in Table 2.

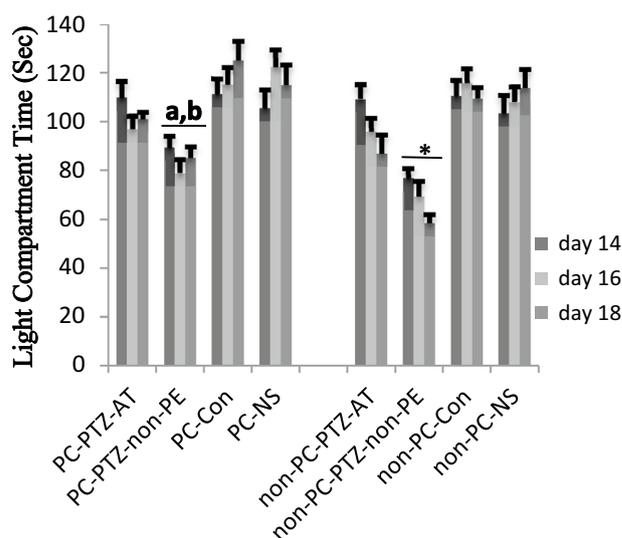


Fig. 2 Effect of aerobic training on anxiety-like behavior. PTZ was given in a dose of 40 mg/kg (i.p.). Two hours after PTZ injection, the amount of time in a light compartment was measured. Values are mean \pm S.E.M for each group. ^a $P < 0.05$ and ^b $P < 0.001$ are associated with the PC-PTZ-non-PE group versus PC-PTZ-AT and PC-Con and PC-NS groups, respectively; * $P < 0.001$ are associated with the non-PC-PTZ-non-PE group versus non-PC-PTZ-AT, non-PC-Con and non-PC-NS groups

Table 2 Amount of time in a light compartment and results of Mann–Whitney’s U test

	Mean \pm SEM	Z	P
Pregnant mice	103.75 \pm 2.56	1.649	0.099
Non-pregnant mice	95.62 \pm 3.12		

The effect of seizure in pregnancy on cognitive function of the adult male offspring

The results of Kruskal–Wallis test to study cognitive difference in the NOR showed that the effect of the group was significant ($\chi^2 = 11.50$, $p = 0.009$; Fig. 3). Using Dunn’s post hoc test, it was observed that male offspring of the PTZ-receiving group without physical activity during pregnancy had a significant difference with male offspring in Kin-Con and Kin-NS groups ($p < 0.05$), but there was no significant difference between male offspring of Kin-PTZ-AT group with the other groups ($p > 0.05$).

Discussion

This study showed the effect of moderate-intensity aerobic training on epileptic conditions in PTZ-treated pregnant and non-pregnant mice which confirmed the efficacy of aerobic

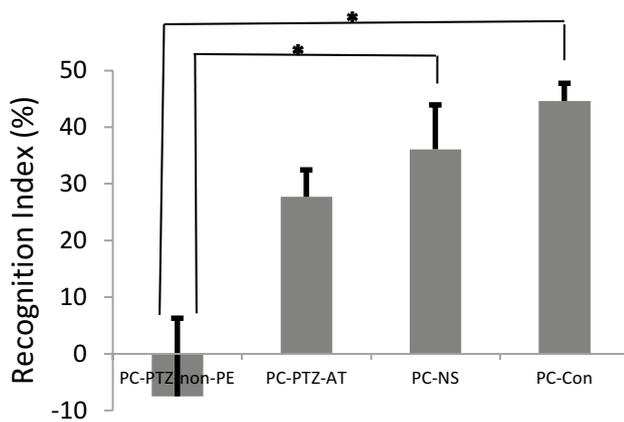


Fig. 3 Effect of seizure during pregnancy on cognitive function of the adult male offspring using NORT. The results are reported based on mean \pm S.E.M. * $p < 0.05$ versus another group

training on seizure control in all subjects. Our results were consistent with the studies that showed the effect of aerobic training on seizure reduction [15, 16] but they were incompatible with the result of the only study on female mice [31].

Physical exercise can regulate neuronal hyper-excitability [13] and stimulate neuropeptide Y in brain [32] which inhibits hippocampal excitability [33]. Other evidence suggests that brain neurotransmission is affected by the training [34]. For example, noradrenaline was increased in the mice with physical activity and the inhibitory effects of this neurotransmitter were observed in the development of kindling [35, 36]. Arida et al. showed physical exercise increased the number of parvalbumin (PV) in epileptic mice [17]. Parvalbumin is a marker of inhibitory interneurons since it is mainly co-localized with the neurotransmitter GABA [37].

We found no different seizure severity between pregnant and non-pregnant mice. Increased levels of progesterone and estrogen during pregnancy [38] could have various influences upon seizure severity. Anti-convulsant effect for progesterone has been reported [39]. But effects of estrogen on seizure is controversial [40]. Battino et al. (2013) have studied human cases; it has been observed that in 70.5% of individuals there is not any variation in pregnancy seizure severity. Meanwhile, in 12% of them severity decrease and in 15.8% severity increase have been seen [41]. Also, Reisinger et al. (2013) have not observed any variation of seizure severity in 44.3 percent of individuals [42].

We were found that seizure-induced by PTZ, increase anxiety in both pregnant and non-pregnant mice without physical activities. PTZ acts as a pro-convulsant by blocking GABAA receptors this reason of anxiety in all subjects [43, 44]. Seizure that was induced with PTZ increases the binding of ligand to AMPA receptors via upregulation of mRNA of the GluR-B subunit [45]. Increasing the density of glutamergic neurons and their receptors increases the

level of anxiety [46]. Also, the oxidative stress was a side effect of seizure [47] that was involved in the pathogenesis of anxiety [48].

The moderate-intensity aerobic activities prevented the increase in seizure-induced anxiety compared to the control groups. Other studies also suggest that treadmill exercise protocols of moderate-intensity (10–15 m/min) reduced the anxiety-like behaviors in rat model of Alzheimer's disease which is examined using the open-field test [49]. Another study showed that moderate-intensity treadmill training (12 m/min) reduces hormonal response to acute mild and severe stress [50]. The effective mechanisms of physical activity in reducing anxiety which can be mentioned are the modulation role of activity of the HPA axis in response to stressors, increased BDNF levels, upregulation of neurogenesis in hippocampus, increased serotonergic and noradrenergic levels and endogenous opioid activity in the brain cited [51].

According to what has been stated so far, the likely reason for the inconsistency between this study and the only research carried out by Kampus et al. (2016) [31] on female rats who did not report the effects of physical activity on seizure activity may be the high intensity of exercises because the intensity of the exercises used in this study, especially in the last weeks, is classified as intensive exercises [52, 53]. Vigorous-intensity exercise can lead to increased oxidative stress [54–56] which increases seizure [57, 58]. Also, Arida et al. (2009) suggested that intense physical activity may increase seizure [59]. In addition, Brown et al. (2007) indicated that protocols of vigorous-intensity exercise; 20 m/min of exercise increases levels of stress hormone corticosterone in the serum of female rats [60] and both single and repeated administrations of the stress hormone corticosterone to epileptic animals increase epileptic activity in the brain and cause susceptibility to seizures [61]. Especially, adult females show enhanced emotional susceptibility to numerous stress paradigms [62, 63]. It has been frequently implicated that sex differences in ventral striatum cause emotional vulnerability in adult females [64, 65].

In addition, non-significant reduction of anxiety rate in pregnant mice compared to non-pregnant mice can be attributed to the increasing attenuation of HPA axis responsiveness as well as the oxytocin secretory response to physical and emotional stresses during pregnancy [66].

The results of the NORT test indicated a cognitive impairment in the offspring of PTZ-treated pregnant mice without aerobic training, which was consistent with the only research conducted on the effect of seizure in pregnancy on cognitive performance of the male offspring performed by Pourmotaaabed et al. (2011). Hypoxia [5] decreased expression of polysialylated neuronal cell adhesion molecule (PSA-NCAM) [19] and increased Bax protein in the hippocampus of male offspring [3] due to seizure in pregnancy, it can be one of

the reasons of cognitive impairment in male offspring in this group. Our results showed that seizure increased anxiety in PC-PTZ-non-PE group. Prenatal stress decreases BDNF expression in the amygdala and hippocampus [67].

One of the reasons for the ineffectiveness of seizure induction during pregnancy on cognitive performance of the male offspring of PC-PTZ-AT group can be related to the reduction of seizure intensity and the prevention of seizure-induced anxiety. Another factor in restoring the cognitive function of the male offspring of PC-PTZ-AT group to the control levels can be attributed to the fact that effects of aerobic activity in pregnancy are related to the offspring. Exercise by pregnant rats has been found to improve spatial learning [24, 68] and short-term memory [69], as well as increase postnatal hippocampal neurogenesis in offspring [70].

Conclusion

In conclusion and considering that adult females show more enhanced emotional susceptibility to stress patterns than males, and it has been observed that high-intensity exercises can increase the amount of stress, it seems that middle-intensity aerobic training not only reduces seizure intensity and seizure-induced anxiety in a rodent model of epilepsy but also prevents cognitive impairment due to induction of seizure during pregnancy. Therefore, one can take advantage of anti-convulsant effects of moderate-intensity aerobic training, especially during pregnancy, and also its beneficial effects on offspring cognitive performance.

Author contributions AS conceived and designed the study. AS, AH and AK were responsible for acquisition, analysis and interpretation of data and drafting of the manuscript. AS was responsible for participant recruitment and contributed to analysis and interpretation of data and correction of the manuscript. AS, AK and NY were involved in critical revision of the manuscript. AS was responsible for statistical analysis and revision of the manuscript. AS and AK performed critical revision of the manuscript regarding important intellectual content. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee (IRB number; 2212538/01) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent All participants provide written, informed consent after being informed about the protocol and purpose of the study. It was approved by the ethics Committee of the Razi university of Kermanshah, Iran.

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