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Effect of magnesium sulfate on hyperthermia and pentylen-tetrazol-induced seizure in developing rats

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ABSTRACT

Objective(s): Febrile seizures (FS) are the most common type of convulsive events among children. Its prevalence has been estimated to be 2-5% in children between 3 months and 5 years old. Also, blood and CSF magnesium levels have been demonstrated to be reduced in children with FS. This study investigates the effect of MgSo4 pretreatment on the behaviors caused by hyperthermia (HT) and effect of these two on pentylen-tetrazol (PTZ)-induced seizure later in life.

Materials and Methods: Thirty two Wistar rats were assigned to 2 groups: saline-hyperthermia-pentylentetrazol (SHP) and magnesium-hyperthermia-pentylentetrazol (MHP). In both groups, HT was induced at the age of 18-19 days old. Before the HT, MHP group received MgSo4 and SHP group received normal saline intraperitoneally (IP). Behaviors of the rats were recorded during the HT. Then, in half of each group (n=8) at the age of 25-26 days old and in other half at the age of 78-79 days, seizure was induced by PTZ.

Results: The HT successfully caused convulsive behaviors in the rats and pretreatment with MgSo4 before HT attenuated HT-induced convulsive behaviors. PTZ-induced seizures a week later was more severe than those of 2 months later.

Conclusion: It can be concluded that pretreatment with MgSO4 inhibits HT-induced seizure and, in a long run, this intervention reduced PTZ-induced seizure later in life.

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Introduction

Febrile seizures (FS) are the most common type of convulsive events among children, which generally occurs in 2-5% between 3 months and 5 years old. This kind of seizure is associated with febrile and increased body temperature. There is no evidence of intracranial infection or previous seizure history (1). This type of seizure is the most common form of pathological brain activity during growth and such a seizure, especially its long type, has been reported to increase the risk of temporal epilepsy in adulthood (2-4). It can also reduce the level of learning and increase susceptibility to epilepsy in adults (5). Convulsion caused by HT in childhood increases susceptibility to temporal lobe epilepsy in adulthood (6). Rajab *et al* (2014) indicated that induction of HT among 10 day old rats decreased their learning at the age of 1.5 months and increased susceptibility to seizure in response to pentylen-tetrazol (PTZ) (5). Genetic and environmental factors such as family history, growth disorders, mother's diseases during pregnancy, types of vaccines, and anything that increases the body temperature like viral infections, respiratory infections, influenza, and even warm baths can play a role in the incidence of this type of seizure (7, 8). Despite many studies which have been conducted in this context, mechanism of FS is not still properly known (7). In addition to these experimental studies, respiratory alkalosis (9), reduction of brain histamine (1), increased levels of cytokines (10, 11), increased calcium influx into the cell (12), and loss of electrolytes such as zinc, magnesium, and iron (13, 14) have been known to be involved in the development of seizure. It has been shown that blocking calcium influx by channel blockers such as nimodipin, tetrodotoxin, and agatoxin reduces the amount and duration of seizure caused by HT (12). Also, there is a connection between FS and magnesium reduction; it has been reported that magnesium levels in CSF and blood are reduced in children with FS (14). Magnesium is one the

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important cations of body, which regulates a variety of body functions involving enzymatic reactions, hormone-receptor binding, opening and closing of calcium channels, entrance and exit of ions through the cell membrane, muscle contraction, activity of nervous system, irritability of the heart, and neurotransmitter release (15). MgSo4 has an anticonvulsant effect and Mg^{2+} containing drugs are used in seizure management among susceptible patients such as pre-eclampsia (15). One of the calcium channels that pass calcium into the cell is N-methyl-D-aspartate receptor (NMDA). Mg^{2+} blocks these channels and decreases the entry of calcium into the cells (15). So, MgSo4 probably could play a role in the prevention of FS. In previous data, behaviors during HT have been studied simultaneously with EEG, which is recorded by the electrodes implanted in the brain, showing that behaviors including hyper activity, sudden immobilization, oral automatism, stiffness of the limbs, and tonic-clonic movements in the animals are in correlation with seizure waves in EEG (16). Based on the present review, no studies were found concerning the effect of pretreatment with MgSo4 on HT-induced behaviors and PTZ-induced seizure. Therefore, this study was designed to investigate the effect of MgSo4 pretreatment on HT-induced behaviors and PTZ-induced seizure in infant rats one week and 2 months later. These time points were selected because, it is likely that a human child may experience a febrile seizure at age of 2 years, then experience another seizure (for any reasons other than fever) later in life either very soon after febrile seizure (for instance, 2 weeks later) or a couple of years later at the age 12-15 years.

Materials and Methods

Subjects

This study was approved by Medical Ethics Committee, Urmia University of Medical Sciences, Urmia, Iran. All the experimental protocols and procedures were complied according to the guidelines of 1975 Declaration of Helsinki as reflected in Guidelines of Medical Ethics Committee, Ministry of Health, Islamic Republic of Iran. The rats were housed in groups of four per cage and kept in standard conditions as follows: Standard 12 hr light/dark cycle, 22±2 °C, and food and water *ad libitum*. On the 21st day of pregnancy, each rat was transferred to a separate cage and the same conditions were applied for all of them. After parturition, the pups were culled to 8 in each litter to reduce the effect of unequal litter size on their development and growth. The pup's birthday was considered the postnatal day 1(P1). On P18 and P19, the pups were randomly divided into 2 groups (16 rats in each group were selected, 2 pups per dam) as follows: Saline-hyperthermia-pentylentetrazol (SHP) group: The pups received 14 ml/kg saline intraperitoneally (IP) and, 30 min later, the HT was induced for 25 min. Then, the rats were subjected to PTZ-induced seizure either a week later or 2 months after HT (on P78-P79). Magnesium-hyperthermia-pentylentetrazol (MHP): 30 min before the HT, the pups received (270 mg/kg, IP) MgSo4. Then, similar to SHP group, the rats were subjected to PTZ-induced seizure on either P25-26 or P78-79.

Hyperthermic chamber

This device has been designed and built at Department of Physiology, Faculty of Medicine, Urmia University of Medical Science (1). In this chamber, a warm air current is blown from the roof of the chamber (at the distance of approximately 40 cm above the rats). The container temperature is monitored near the chamber's wall. Air temperature is maintained at ±1°C by feedback electronics, which automatically adjusts heating levels several times per second in response to the air temperature. When a lower air temperature is required to prevent animals from overheating, the system adapts itself within seconds. In this way, the temperature inside the chamber is kept at a constant interval. In this study, the temperature inside the chamber was considered 54 ±2˚C.

Induction of hyperthermia

The HT was induced by a hot air current as described previously by Baram *et al* (16) and Gholipoor *et al* (1). Behaviors of each rat were closely monitored during HT. Due to the lack of equipment, EEG recording was not performed. All the pups were kept in their dam until 35 min prior to the experiment. Each rat was weighed and received an injection of either saline (14 ml/kg) or MgSo4 (270 ml/kg) IP with equal volume. Thirty min later, the rats were moved to a chamber where the temperature was already brought to the desired level (54 ±2˚C). Immediately before and after the HT, core body temperature of the rats was measured by a rectal probe. Behaviors of the rats were monitored and recorded for 25 min and were then categorized according to Table 1. The latency of each behavioral stage was determined and total score of seizure was calculated. For instance, if a rat showed one behavior from an identical stage, the score for that stage was considered and, if the rat showed several behaviors of a stage, the score for that stage was multiplied by the number of behaviors and finally all the values were summed. In this study, because tonic-clonic seizure was found in none of the rats, it was ignored in the calculation of the total score (1). For example, if a rat showed hyperactivity (Stage 1), ataxia (Stage 2), rotational motion (Stage 3), and tremor (Stage 3), the total score was 1+2+ (2×3)=9. Total score (TS) =$\sum$ (S.NB), where S stands for stage and NB stands for the number of behaviors at the stage.

Table 1. Classification of rat behaviors during HT

Stage	Behavior	Description
0	Normal	Normal explorative behavior
1	Hyperactivity	Hyperactive behavior, jumping, and rearing
2	Immobility Ataxia	Sudden complete immobility (duration: 3–10 sec), unsteady, jerky gait
3	Circling	Running in tight circles (approximately two circles/sec)
	Shaking	Whole-body shaking
	Clonic seizures	Contractions of hindlimbs and forelimbs with reduced consciousness
4	Tonic–clonic convulsions	Continuous tonic–clonic convulsions

The rats were kept in the hyperthermic chamber for 25 min. Then, they were removed from the chamber and their core body temperature was recorded (final Tem). Afterwards, the rats were partly submerged in the water at room temperature to quickly normalize their core body temperature. They were transferred to their dams until inducing seizures with PTZ on P25-26. On the same day, the rats which were considered for the study on P78 -79 were housed 4 rats per cage and kept in standard conditions until P78.

PTZ-induced seizure

In the morning between 800 and 1100 either on P25-26 or P78-79, the rats received PTZ (45 mg/kg, IP) and were transferred to a glass chamber (30 ×30 ×30 cm) to measure their behaviors. Convulsive behaviors of the rats were monitored for 60 min and seizure score was determined for each rat according to the 5 stage criterion by Racine *et al* (17): 0=Normal; 1=Immobilization, sniffing; 2=Head nodding, facial and forelimb clonus (short myoclonic jerk); 3= Continuous myoclonic jerk, tail rigidity; 4=Generalized limbic seizures with kangaroo posture or violent convulsion; 5=Continuous generalized seizures (tonic or clonic-tonic convulsions). In addition, latency to the first seizure, first tonic-clonic seizure, duration of tonic-clonic seizures, and latency to the first legs extension were also observed and recorded.

Data analysis

Data distribution was controlled using Kolmogorov–Smirnov test. The data that were normally distributed were analyzed using parametric techniques. The t-student was used for two-group comparison and One-way Analysis of Variance (ANOVA) was used for multiple comparisons. Data related to the base temperature, final temperature, body weight, latency to Stage 3, and total score of seizure were normally distributed. The data that were not normally distributed (values of some seizure parameters) were analyzed by non-parametric tests. Mann Whitney U test was used for two-group comparison. The incidence of tonic-clonic seizure and mortality rate were analyzed using K^2 test. The results were expressed as mean ± SEM and $P< 0.05$ was considered significant.

Results

Effect of MgSo4 on hyperthermia-induced behaviors

The mean body weight of the rats in SHP group was 28.29±0.86 g and, in the MHP group, it was 28.97±0.90, which were not statistically significant. The mean of basic temperature of rats in the SHP group was 35.92±0.19 and, in the MHP group, it was 35.96±0.20 °C, which were not statistically significant. Core body temperature of the rats which received hyperthermia increased, but did not rise to above 41 °C during the experiment (Table 2). The rats were exposed to hyperthermia on P18-19 and then weighed one week and two months later.

In the assessment of hyperthermic behaviors, after entry into the chamber, the rats had a normal exploratory behavior (Stage 0) which quickly turned into hyperactivity behavior and sometimes the rats showed jumping and rearing frequently (Stage 1). Then, all activities of the rats stopped and stayed immobile for a while (Step 2). In some of the rats, oral automatism was seen (Step 2). Some rats initially showed the behaviors of Stage 2 without showing behaviors of Stage 1. Most of the rats had imbalance in motions (Step 2) or circular motion (Step 3). Afterwards, contraction of limbs and

Table 2. Mean of body weight, base temperature, and final temperature in 18 or 19 day old rats receiving HT and body weight one week and 2 months later

Groups	Body weight (P18-19)	Base Tem	Final Tem	Body weight (P25-26)	Body weight (P78-79)
saline	28.29 ± 0.86 g	35.92 ± 0.19˚C	40.00± 0.10˚C	47.18 ± 1.08 g	174.12± 3.06 g
Mgso4	28.97 ± 0.90 g	35.96 ± 0.20˚C	39.73±0.16 ˚C	49.56± 2.00 g	178.12 ± 6.03 g

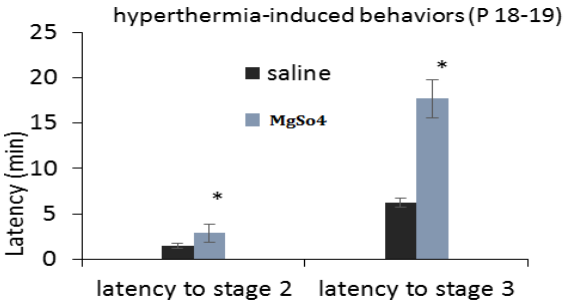

Figure 1. Pretreatment with MgSO4 in the rats at P18-19 significantly increased latency to stages 2 and 3 of hyperthermic behavior (*P*=0.04 and *P*=0.02, respectively); * indicates significant difference from saline group

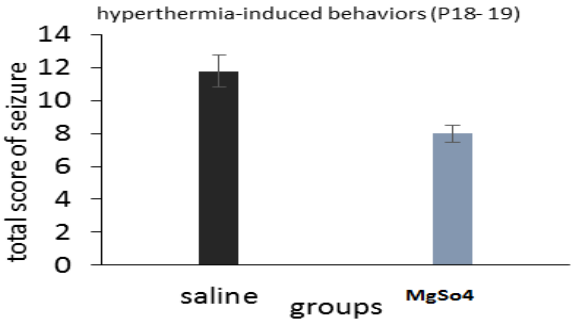

Figure 2. Pretreatment with MgSO4 in 18 and 19 day old rats non-significantly reduced the total score of seizure in HT rats

tremor of abdominal muscles were seen. None of the rats experienced tonic-colonic seizures (Stage 4) and none were dead in HT. Latency to stages 2 and 3 significantly increased in MHP group compared with SHP group (Figure 1).

On the other hand, total score of seizure decreased in MHP group compared with SHP group; but, this reduction was not statistically significant (Figure 2).

Effects of MgSo4 and hyperthermia on PTZ-induced seizure on P25-26

Following the injection of PTZ, behaviors of the rats were monitored accurately. Some of the rats initially showed immobility (Step 1). In others, head nodding (Step 2) was seen. Sudden opening of legs was observed frequently which was scored as Stage 3. In some of the rats, tail extension and clonus of face or hands (Step 3) were seen. Some of them entered Stage 4 (including intensive seizures and involuntary jumps). Some others entered Stage 5 and continued tonic-clonic seizure and loss of consciousness. In this study, none of the rats showed tonic-clonic seizures more than once. None of them were dead due to PTZ-induced seizure.

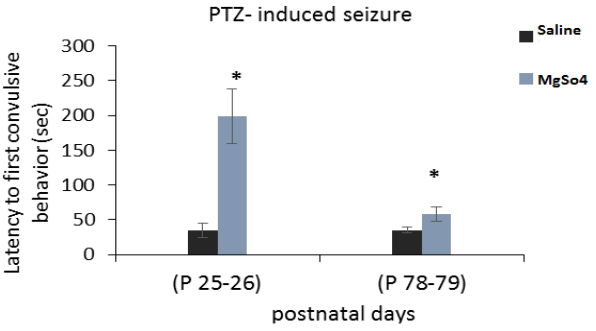

Figure 3. Pretreatment with magnesium sulfate before HT in rats on P18-19 significantly increased latency to the first convulsive behavior caused by PTZ one week and 2 months later (*P*=0.005 and *P*=0.001, respectively); * indicates significant difference from saline group at the same age

Latency to the first convulsive behavior significantly increased in MHP group compared with SHP group (Figure 3). There was a significant difference between SHP and MHP groups one week after hyperthermia in terms of latency to tonic-clonic seizure caused by PTZ (Figure 4).

Duration of tonic-clonic seizure in SHP group was significantly more than that of MHP group (Figure 5).

In MHP group, one out of eight rats (1/8) and, in SHP group, five out of eight (5/8) rats showed tonic-clonic seizure which was statistically significant (K^2, *P*=0.039).

Total score of seizure in SHP group was significantly higher than that of MHP group (Figure 6).

Pretreatment with MgSo4 before hyperthermia in the rats on P18-19 significantly increased latency to tonic-clonic seizure on P25-26 (*P*=0.02); but, it was not effective on P78-79 (Figure 4). Latency to the first opening of legs showed a non-significant rise in MHP group compared with SHP group (Figure 7). Administration of MgSo4 before hyperthermia in the rats on P25-26 significantly decreased the duration of tonic-clonic seizure induced by PTZ on P25-26 (*P*=0.02), but not on P78-79 (Figure 5).

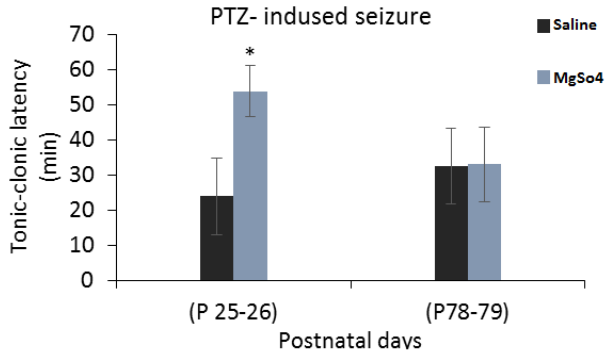

Figure 4. Pretreatment with MgSo4 before HT in rats on P18-19 significantly increased latency to tonic-clonic seizure one week later (*P*=0.02), but not 2 months later; * indicates significant difference from saline group at P25-26

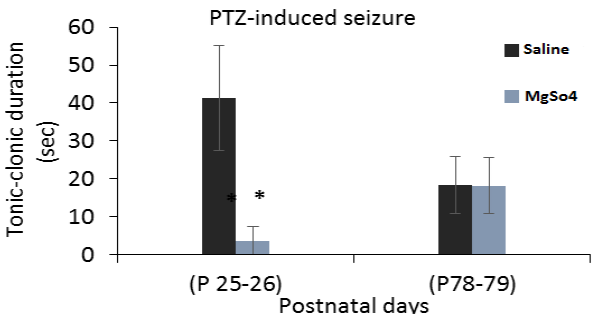

Figure 5. Pretreatment with MgSo4 before HT in rats on P18-19 significantly decreased (*P*=0.02) duration of tonic-clonic seizure caused by PTZ one week later, but not 2 months later; * indicates significant difference from saline group at P25-26

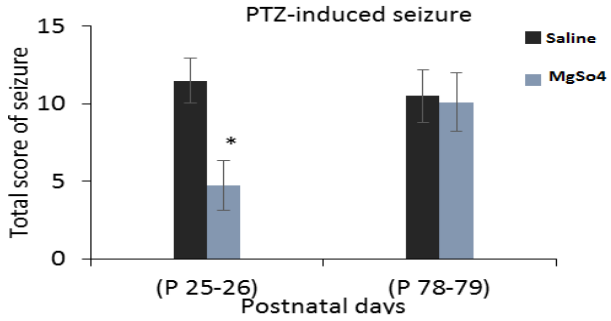

Figure 6. Pretreatment with MgSo4 before HT in rats on P18-19 significantly decreased total score of seizure caused by PTZ (*P*=0.01) on P25-26, but not 2 months later; * indicates significant difference from saline group at P25-26

PTZ-induced seizure on P78-79

On P78-79, the rats were weighed; but, there was no significant difference between SHP and MHP groups (Table 2). Latency to the first convulsive behavior was significantly longer in SHP than MHP groups (*P*=0.001) (Figure 3). Latency to legs opening was significantly longer in MHP than SHP groups (*P*=0.006) (Figure 7). Latency to tonic-clonic seizure (Figure 4), duration of tonic-clonic seizure (Figure 5), and total score of seizure were not significantly different in both groups (Figure 6). In both groups, four of the eight rats showed tonic-clonic seizure.

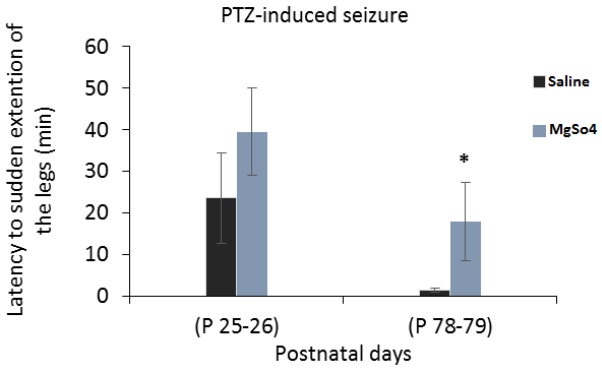

Figure 7. Pretreatment with MgSO4 before HT in rats on P18-19 significantly increased latency to sudden legs opening in PTZ-induced seizure on P78-79 (*P*= 0.01). * indicates significant difference from saline group at the same age.=

Discussion

In this study, pretreatment with MgSo4 significantly attenuated HT-induced seizure on P18-19 in the rats. PTZ-induced seizure was induced on P25 and P78. Pretreatment with MgSo4 prior to HT reduced PTZ-induced seizure considerably on P25 and somewhat on P78. Induction of HT was performed based on Baram *et al 's* model (1) that was also described by Gholipoor *et al* (16). HT-related behaviors that were seen in the current study were in line with the findings by these researchers. Also, MgSo4 remarkably reduced convulsive behaviors caused by HT. Temperature of HT chamber was initially considered at 52-48°C according to the previous studies (1, 5). But, this temperature could not induce convulsive behavior above Stage 2, with the exception of few cases. So, the chamber's temperature was considered 54±2° C. Even this temperature could not induce tonic-clonic seizure that can be attributed to shorter time of heating and higher age of rats in this study compared to the previous investigations. This finding confirmed HT was an age-related process, indicating that HT-related behaviors tightly depend on the duration of HT. Because of high mortality rate at severe HT (1) and in order to keep the rats alive for the second phase of study on P25 and P78, the time of HT was considered (25 min) shorter than the previous studies (30 min). As a result, no death occurred after HT.

Magnesium sulfate is a drug containing Mg^{2+} which is known as the antagonist of NMDA channel and reduces calcium influx into the cell by blocking these channels. The entry of calcium into the cell has been known as one of the possible causes of FS in previous study (12). MgSo4 is likely to reduce HT-induced seizures by decreasing entry of calcium into the cell. MgSo4 is frequently used for the treatment or prevention of any kind of seizures, especially those caused by eclampsia (18-21). In most of the preeclamptic patients, pretreatment with MgSo4 can control disease and prevalence of eclampsia or at least reduce its complications (18-21). From a general point of view, basic mechanisms of any kind of seizures are almost the same; MgSo4 can be announced for seizure control and a useful remedy for FS. Many studies have suggested that seizures occur when brain's inhibitory system such as GABA is decreased and activity of excitatory systems including glutamate is increased (22-25). The result of the current study was consistent with the findings of previous investigations, since pretreatment with MgSo4 almost completely inhibited convulsive behaviors of HT. As mentioned earlier in this study, PTZ-induced seizure was induced one week and two

months after HT. Pretreatment with MgSo4 before HT remarkably reduced convulsive behaviors of PTZ one week later and mildly two months later. It has been reported that FS early in life increases susceptibility to seizures or epilepsy later in life. In support of this finding, Rajab *et al* induced HT in newborn rats on P10 and tested susceptibility to seizure on P45; they showed that susceptibility to seizure increased (5). In the present study, threshold of seizure was not measured. Thus, from the results of this study, the susceptibility to seizures and threshold of its occurrence cannot be easily discussed. In this case, the results of the present study (on some of the convulsive behaviors) caused by PTZ were not consistent with those of the previous study (5). Such a difference can be probably attributed to shorter HT time and lack of tonic-clonic seizure during HT in the current study, which might cause long-term effects of severe HT seizures not to completely appear later in life. However, the results of this study showed that pretreatment with MgSo4 reduced the adverse effects of HT on some convulsive behaviors of PTZ in adulthood. Kliouеva *et al* previously showed that threshold of PTZ-induced seizure varied at different ages of Wistar rats as the threshold was increased from P10 to P25 and then, by increasing age, the threshold was reduced (26). Other studies have reported age-related susceptibility to seizures (27-29). The findings of the present study were consistent with the results of these investigations. Also, the effect of MgSo4 on HT in attenuating PTZ-induced seizure followed this pattern. Huge entry of calcium into the cells is known as one of the reasons of cell death in seizure and many other brain insults (30). It is likely that blocking NMDA channels with MgSo4 in HT by reducing the entry of calcium into the cell prevents cell death and has the potential to reduce seizure at older ages. In several models of seizure, damage of brain tissue following seizure has been proven (31-33). Perhaps high calcium influx in HT leads to cell depolarization as well as increased irritability and causes HT-induced seizure. In addition, an increase in intracellular calcium concentration in HT causes cell death and permanent damage to the brain tissue which, in turn, increases susceptibility to seizure in adulthood (5, 33). Pretreatment with MgSo4 in HT, by reducing the entry of calcium into the cell, decreases depolarization and cell death during HT and also reduces susceptibility to seizure in adulthood.

It can be concluded that pretreatment with MgSo4 before HT affects HT-induced behaviors and decreases the incidence and severity of seizures during HT. Thus, it probably prevents neural damage or at least reduces its extent and, in turn, reduces susceptibility to seizure at older ages. Further and more detailed studies are needed to clarify the underlying mechanisms in this regard.

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Ethical approval

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest statement

The authors have no conflicts of interest to declare regarding the study described in this article and the preparation of the article.

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