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Inhibitory effects of chronic administration of vitamin D_3 on pentylenetetrazole-induced seizures in mice

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ABSTRACT

Vitamin D_3 as a neuroactive steroid hormone plays an important role in the nervous system. Recent clinical and experimental studies have shown an association between vitamin D-related disorders and epilepsy. Therefore, this study was designed to examine the effects of chronic administration of vitamin D_3 on pentylenetetrazole (PTZ)-induced seizure in mice.

This interventional study was conducted on 120 mice in 12 groups. Two control groups acutely and chronically received a mixture of almond oil and paraffin; three groups were acutely given vitamin D_3 at doses of 2000, 4000 and 6000 IU/kg; three groups chronically received vitamin D_3 with similar doses for two weeks and two groups chronically and acutely received a sub-effective dose of vitamin D_3 and diazepam. Slow intravenous infusion of PTZ (5 mg/mL) was performed at a constant rate (0.3 mL/min) via an infusion pump to induce clonic and tonic seizures.

Acute injection of different concentrations of vitamin D_3 (2000, 4000 and 6000 IU/kg i.p.) did not significantly increase a seizure threshold. However, a seizure threshold in the groups chronically treated with 4000, and 6000 IU/kg of vitamin D_3 was significantly higher than that in the control group ($P < 0.001$). Moreover, a combination of the sub-effective dose of vitamin D_3 (2000 IU/kg) and diazepam (0.1 mg/kg) significantly increased seizure threshold. Our findings suggest that administration of vitamin D supplement can be considered as a potential add-on treatment in seizure and due to the vitamin D deficiency results from the long-term use of most anti-seizure drugs, this supplementation becomes more important.

1. Introduction

The most biologically active form of vitamin D in humans is vitamin D3 (cholecalciferol), which is a fat-soluble steroid pre-hormone. For several decades, the role of vitamin D was thought to be confined to Ca^{2+} and phosphate homeostasis, and to bone formation and maintenance, however, current evidence suggests a wider biological role for Vitamin D3 in the human brain and nervous system (Garcion et al., 2002). The roles of Vitamin D have been reported in different neurological disorders such as Alzheimer's and Parkinson's disease, multiple sclerosis schizophrenia and affective disorders (Taghizadeh et al., 2014). A neurological role of Vitamin D is further supported by the presence of Vitamin D-specific receptors and enzymes in neurons and glial cells throughout the brain, in the spinal cord, and in the peripheral nervous system (Ghaderi et al., 2017). There is also evidence linking vitamin D disorders to epilepsy. For the first time, anticonvulsant properties 1,25-dihydroxyvitamin D3 have been reported by Siegel et al. (1984), who found that the administration of active form of vitamin D3 results in the elevation of hippocampal seizure threshold levels in rats. In addition, in an animal study by Kalueff et al. (2005) have shown the anticonvulsant effects of 1,25-dihydroxyvitamin D in chemically induced seizures in mice (Kalueff et al., 2005). Although vitamin D deficiency is known to be highly prevalent among epileptic patients, only a few studies evaluate the effect of vitamin D on seizure control. In a pilot study, the serum 25-hydroxy-vitamin D (25(OH)D) levels were measured and normalized by the administration of vitamin D3 in 13 patients with pharmacoresistant epilepsy. They found that seizure numbers significantly decreased upon vitamin D3 supplementation and concluded that the normalization of serum vitamin 25(OH)D level has an anticonvulsant effect (Holló et al., 2012). Vitamin D3 decreases the expression of certain proconvulsant cytokines, such as IL-1β and TNF-α (Pendo and DeGiorgio, 2016). Vitamin D3 can also

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increase the expression of anticonvulsant growth factors such as nerve growth factor (Wion et al., 1991). Vitamin D3 may change plasma and brain calcium concentrations through enhancement of calcium absorption from the intestine, which may decrease neuronal excitability and reduce the risk of seizure. It was also suggested that the rapid anticonvulsant effect of vitamin D3 could be mediated through its ability to fine-tune Ca2+ and Cl − currents across neuronal membranes. Taken together, this led us to propose the possible anticonvulsant effect of vitamin D. In the present study, the effects of acute and chronic administrations of vitamin D3 alone and in combination with a sub-effective dose of diazepam (as a typical anti-seizure drug) were evaluated on pentylenetetrazole-induced seizure in mice.

2. Methods

2.1. Study design

In this interventional study, 120 Balb/c male mice, aged 2–3 months and weighing 25–30 g, were housed and bred in the animal room of Kashan University of Medical Sciences (Kashan, Iran). They were kept in polypropylene cages (six animals per cage), at constant temperature of 22 ± 2°C and humidity of 50%–55%, with an automatically controlled 12:12 h light/dark cycle. All animals were fed regular mice chow and water *ad libitum* (Jafari-Sabet et al., 2013). Animals were randomly divided into the following groups (n = 10 in each group).

1 Acute control group, which received only a single injection of 20 IU of almond oil and paraffin mixture in half an hour before the beginning of the PTZ infusion.
2 Chronic control group, which received the same injection once a day for 14 days; PTZ-infusion began on the last day after the injection of almond oil and paraffin mixture.
3 Three groups acutely received 2000, 4000 and 6000 IU/kg of vitamin D3 in half an hour before the PTZ infusion.
4 Three groups chronically received 2000, 4000 and 6000 IU/kg of vitamin D3 for 14 days prior to seizure induced by PTZ (Siegel et al., 1984; Williamson et al., 2017).
5 Two groups received diazepam at concentrations of 0.1 and 1 mg/kg.
6 Two groups received combination of a sub-effective dose of diazepam and vitamin D3.

Vitamin D3 with concentrations of 2000, 4000 and 6000 IU was prepared by mixing almond oil and paraffin. Diazepam (0.1 mg/kg and 1 mg/kg) was also prepared. An intraperitoneal injection was performed half an hour before the test in each group (Hamidi et al., 2014).

2.2. Seizure induction

Pentylenetetrazole (PTZ) was dissolved in the heparinized sterile saline (0.9%) solution to prepare a fresh solution with a concentration of 5 mg/mL. Intravenous injection was performed in the lateral tail vein. The infusion rate of administered PTZ was 0.3 mL/min. Before testing, each mouse was weighed, placed in a clear acrylic plastic restrainer and its tail was immersed in a warm water bath (40–45 °C) for 60 s to dilate the tail veins. A dental carpule (27 G, Heraeus Kulzer, Germany), which was connected by a polyethylene tube (No. 10) to a 50 mL syringe prefilled with the heparinized PTZ solution, was used. The needle was inserted into the mid length of the lateral tail vein. After verifying the proper insertion by the appearance of blood in the infusion tube, the needle was secured to the tail using a special tape. The syringe was held in the adjustable motor driven infusion pump (TOP Syringe Pump, Japan). During the infusion period, the animal could move freely in the Plexiglas observation box with the aid of an attached cannula. Each animal was observed throughout the infusion period. The duration time between the start of infusion and onset of the seizure stages was recorded in seconds and then converted to the threshold convulsant dosage (i.e. mg of drug per kg of body weight). The threshold concentration in mg/kg for the appearance of seizure signs was calculated using the following formula (Kouchaki et al., 2016; Mesdaghinia et al., 2010):

$$\frac{Rate(mL/min) \times Time(s) \times Concentration(mg/mL) \times 1000}{60 \times Bodyweightofanimal}$$

2.3. Statistical analysis

Results are expressed as mean ± standard error of the mean (SEM). Statistical analysis of the results was performed by one-way ANOVA for seizure thresholds of each convulsion stage followed by the Tukey's test for multiple comparisons. P-value less than 0.05 was considered as statistically significant (Banafshe et al., 2007).

3. Results

3.1. Effect of acute vitamin D_3 administrations on seizure threshold

The mean clonic seizure threshold in the control group was 79 ± 2.76 mg/kg, which showed no significant difference compared to the mean seizure threshold in the groups received 2000 IU/kg (78 ± 2.65 mg/kg), 4000 IU/kg (82 ± 2.16 mg/kg) and 6000 IU/kg (86 ± 3.76 mg/kg) of vitamin D_3 (Fig. 1). The mean threshold for tonic seizures in the acute model for vehicle was 131.5 ± 4.3 mg/kg and these mean values in the groups received 2000, 4000 and 6000 IU/kg vitamin D_3 were 150.5 ± 8.2, 144.4 ± 6.2 and 138.2 ± 7.7 mg/kg, respectively. The difference among the groups was not statistically significant (Fig. 2).

3.2. Effect of chronic vitamin D_3 administrations on seizure threshold

The mean clonic seizure threshold in the chronic model was 78 ± 3.7 mg/kg in the vehicle group and it was 85.1 ± 3.7 mg/kg in the group received 2000 IU/kg of vitamin D_3, which was similar to the vehicle group. The mean seizure threshold in the group received 4000 IU/kg of vitamin D_3 was 104.3 ± 3.1 mg/kg, which was significantly higher than that in the vehicle group ($P < 0.001$) and it was 99.5 ± 2.9 mg/kg in the group received 6000 IU/kg of vitamin D_3, which was significantly higher than that in the vehicle group ($P < 0.01$) (Fig. 3). The mean tonic seizure threshold in the chronic model for vehicle was 130 ± 3.7 mg/kg; the mean values in the groups received 2000, 4000, and 6000 IU of vitamin D_3 were 173.5 ± 7 mg/kg, 179.9 ± 4 mg/kg and 176.5 ± 4.3 mg/kg, respectively, which were significantly higher in all the three groups than in the vehicle group ($P < 0.001$) (Fig. 4).

3.3. Effect of acute diazepam administrations on seizure threshold

To determine the minimum effective and sub-effective doses of diazepam in PTZ-induced tonic-clonic seizures, this drug (1 and 0.1 mg/kg i.p.) was administered acutely half an hour before the PTZ infusion. The mean clonic seizure threshold in the mice receiving diazepam 1 mg/kg was 123.8 ± 8 mg/kg, which was significantly more than that in the control group ($P < 0.001$). However, 0.1 mg/kg of diazepam had no significant effect on the seizure threshold (Fig. 5). The mean tonic seizure threshold in the group received 1 mg/kg diazepam was 212 ± 5.6 mg/kg, which was significantly higher than that in the control group ($P < 0.001$). However, the mean tonic seizure threshold in the group received 0.1 mg/kg diazepam was 141 ± 6.5 mg/kg (Fig. 6).

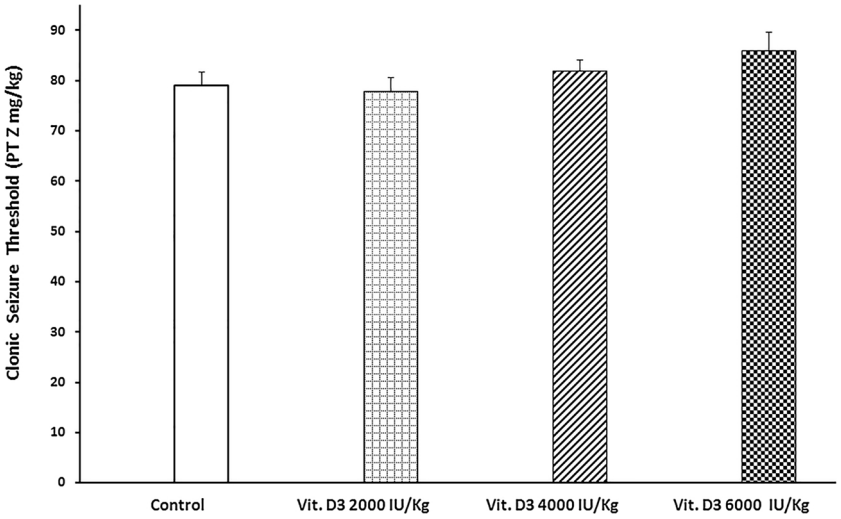

Fig. 1. comparison of mean clonic seizure threshold doses between acute treatment with vitamin D_3 (2000, 4000 and 6000 IU/kg i.p.) and vehicle. The results are expressed as Mean ± S.E.M., n = 10 in all groups.

3.4. Effect of a combination of diazepam and vitamin D3 on seizure threshold

The mean clonic seizure threshold was 88 ± 2 mg/kg in the group received the combined dose of 0.1 mg/kg diazepam and 6000 IU/kg vitamin D3 in the acute form, which showed no significant difference compared to the vehicle group (77 ± 2 mg/kg) (Fig. 7). The mean tonic seizure threshold in the group received the combined dose of 0.1 mg/kg diazepam and 6000 IU/kg vitamin D_3 in the acute form was 164 ± 8.4 mg/kg, which was not significantly different from that of the vehicle group (Fig. 8). Also, the mean clonic seizure threshold in the group received the combined dose of 0.1 mg/kg diazepam and 2000 IU/kg vitamin D_3 in the chronic form was 108 ± 6.3 mg/kg, which was significantly higher compared to that of the vehicle group (77 ± 3 mg/kg) ($P < 0.001$) (Fig. 9). The mean tonic seizure threshold in the group received the combined dose of 0.1 mg/kg diazepam and 2000 IU/kg vitamin D3 was 196 mg/kg, which was significantly higher compared to that of the vehicle group (142 mg/kg) ($P < 0.001$) (Fig. 10).

4. Discussion

In this study, the effects of vitamin D_3 administration in acute (half an hour before seizure) and chronic (two weeks before induction of seizure) regimens were examined on seizure threshold in mice and it was found that administration of 2000, 4000 and 6000 IU/kg of vitamin D half an hour before seizure induction had no effect on clonic-tonic seizure threshold. But, chronic administration of 4000 and 6000 IU/kg of vitamin D significantly increased the clonic seizure threshold and the chronic administration of 2000, 4000, and 6000 IU/kg of vitamin D significantly increased the tonic seizure threshold. Concurrent administration of the ineffective dose of vitamin D (2000 IU/kg) and diazepam resulted in a significant increase in the seizure threshold. In fact, vitamin D_3 potentiates the effect of diazepam in control of seizures.

Limited studies have been done to evaluate the effects of vitamin D on seizure. Role of 1,25-dihydroxyvitamin D (calcitriol) in chemically induced seizure was investigated in mice. Calcitriol was subcutaneously injected 40 min before the induction of seizure. Finally, based on the Racine's Scoring System, it was found that severity of seizure was lower in mice treated with calcitriol (Kalueff et al., 2005).

Results of this study showed that calcitriol had a direct anti-seizure effect. This study is generally consistent with our results but in our study, acute injection of different concentrations of vitamin D_3 (2000, 4000 and 6000 IU/kg i.p.) did not increase the seizure threshold significantly. This difference is due to the administration of very high

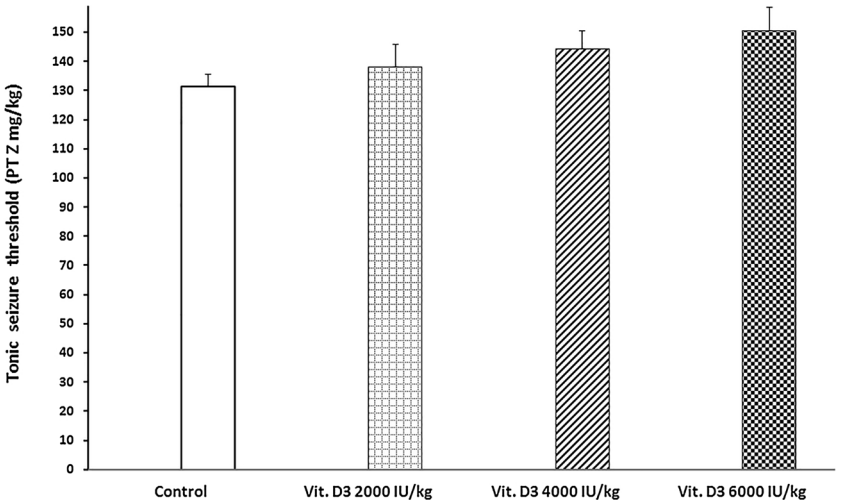

Fig. 2. comparison of mean tonic seizure threshold doses between acute treatment with vitamin D_3 (2000, 4000 and 6000 IU/kg i.p.) and vehicle. The results are expressed as Mean ± S.E.M., n = 10 in all groups.

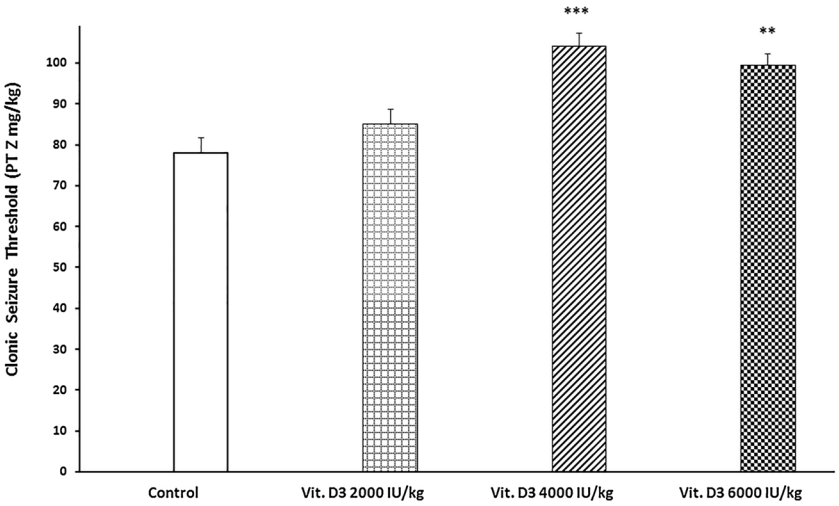

Fig. 3. The comparison of mean clonic seizure threshold doses between chronic treatment with vitamin D_3 (2000, 4000 and 6000 IU/kg i.p.) and vehicle. The results are expressed as Mean ± S.E.M., n = 10 in all groups. ** P < 0.01 and *** P < 0.001 versus vehicle.

dosage (33 µg per mice is equal to 52,000 IU/kg) that it can explain the reason of a single-dose efficacy of calcitriol. Meanwhile, our data showed that the chronic administration of lower dosage of vitamin D (4000 IU/kg) significantly increased the tonic and clonic seizure threshold and this dosage is more practical and there is no concern about side effects and toxicity. Efficacy of the chronic administration of vitamin D (4000, and 6000 IU/kg) and ineffectiveness of acute dosing suggest that slow genomic actions of vitamin D are possible anticonvulsive mechanisms but the anti-seizure effect of an acute high dosage of calcitriol (52,000 IU/kg), which has been reported by Kalueff supports the rapid non-genomic action of calcitriol. In another pilot study, vitamin D levels were measured in 25 epileptic patients and vitamin D deficiency was normalized. The number of seizures was significantly reduced in the group received vitamin D supplement and it was stated that the normalization of vitamin D levels had anti-seizure effects (Holló et al., 2012). The interaction between vitamin D and anti-seizure medications such as lamotrigine and topiramate, in the maximum electro-shock test in mice has also been studied; it has been shown that vitamin D not only has anti-seizure effects, but also strengthens the effect of some anti-seizure medications (Kinga et al., 2015; Borowicz et al., 2007).

A lack of a satisfactory response to pharmacotherapy of epilepsy is a major neurological problem. One of the effective approaches for controlling pharmacoresistant seizures is represented by administration of supplement and nutritional induction of ketogenesis. Ketogenic diets are increasingly used all over the world, but this nutritional treatment (see Giordano et al., 2014 for a review) also causes nutritional deficits, which hamper its efficacy. One of the most remarkable nutritional deficits is vitamin and mineral deficiency (Marchiò et al., 2018) and it has been suggested that a possible cause of the described worsening in seizures occurring under the ketogenic diet could be a lack of adequate supplementation with vitamin D (Lucchi et al., 2017).

The functions of vitamin D are mediated through the nuclear vitamin D receptor (genomic effects) and specific membrane receptors (none-genomic effects) (Cui et al., 2017). Compared to its genomic actions, the non-genomic effects of vitamin D in the brain have been explored to a much less extent. Regulation of calcium channels and activation of protein kinase C and mitogen-activated protein kinase pathways are some of the non-genomic signal transduction events triggered by calcitriol (Weng and Chung, 2016).

More recently, calcitriol has been reported to rapidly modulate synaptic transmission in juvenile gonadotrophin-releasing hormone neurons. Using the whole-cell patch clamp technique, it was shown that the acute application of vitamin D decreased the inward currents induced by the excitatory neurotransmitters NMDA and kainate, in a reversible and action potential-independent manner (Bhattarai et al., 2017). Since

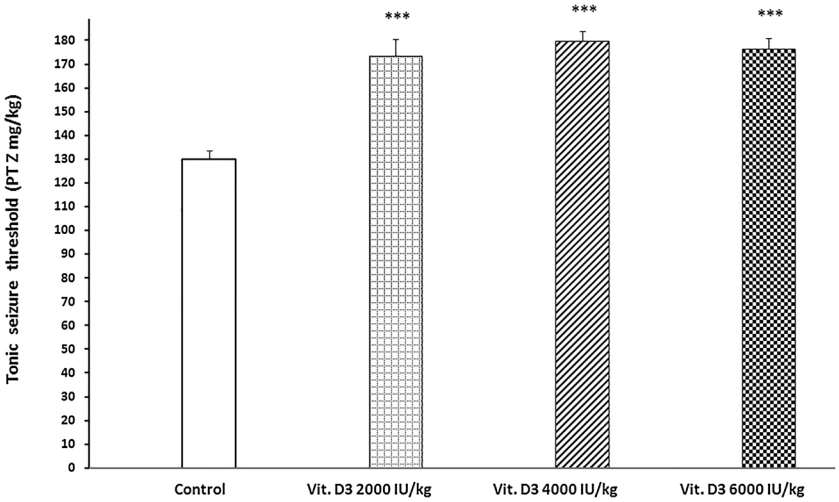

Fig. 4. Comparison of mean tonic seizure threshold doses between chronic treatment with vitamin D_3 (2000, 4000 and 6000 IU/kg i.p.) and vehicle. The results are expressed as Mean ± S.E.M., n = 10 in all groups. *** P < 0.001 versus vehicle.

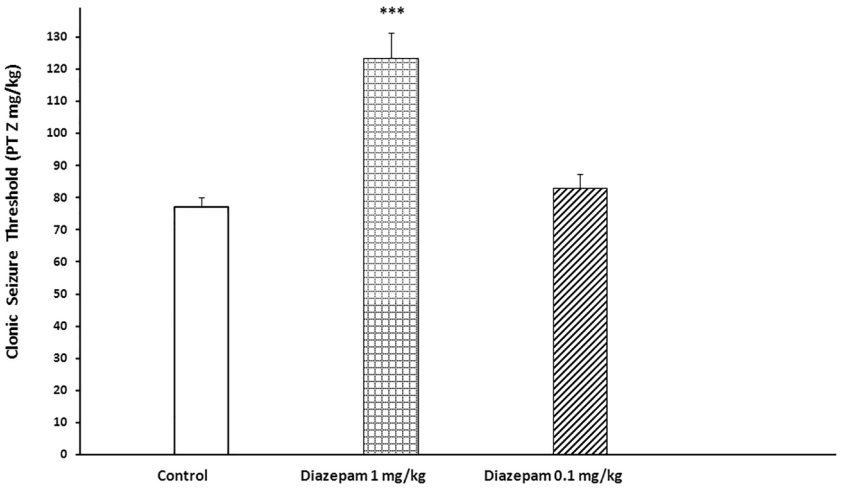

Fig. 5. Comparison of the mean dose of the clonic seizure threshold in the animals receiving diazepam (1 and 0.1 mg/kg i.p.) with the control group. The results are expressed as Mean ± S.E.M., n = 10 in all groups. ***P < 0.001 versus control group.

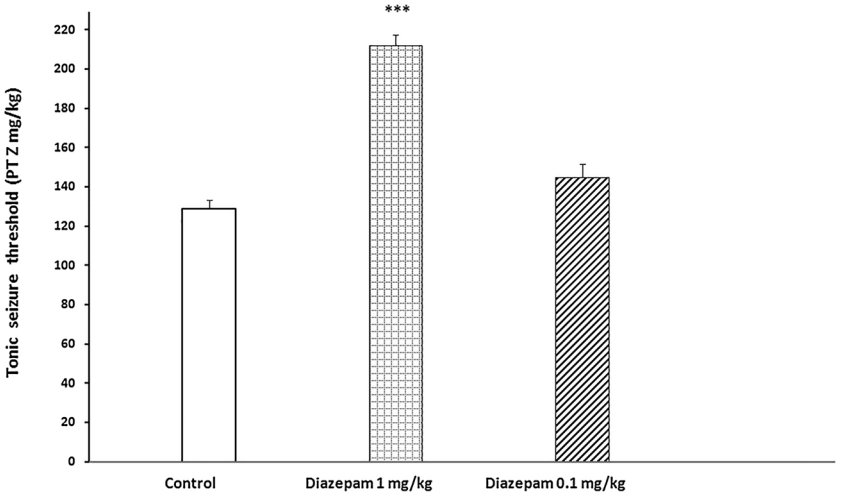

Fig. 6. Comparison of the mean dose of the tonic seizure threshold in the animals receiving diazepam (1 and 0.1 mg/kg i.p.) with the control group. The results are expressed as Mean ± S.E.M., n = 10 in all groups. ***P < 0.001 versus control group.

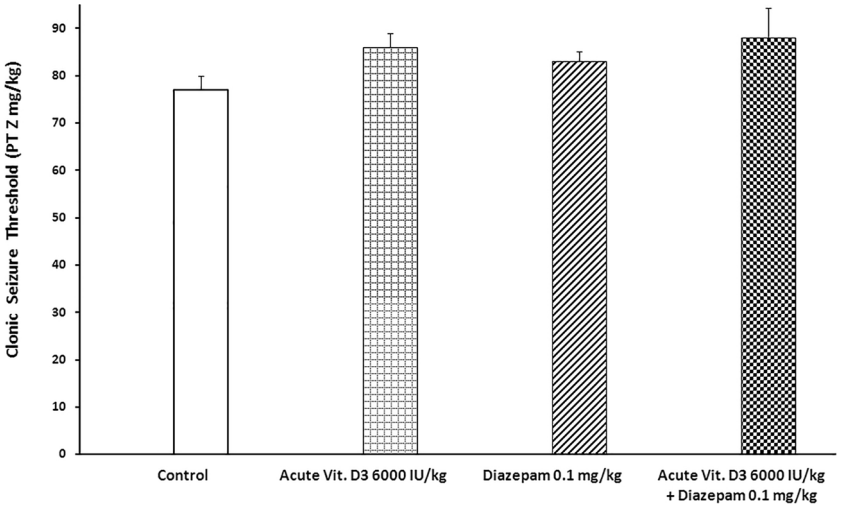

Fig. 7. The mean clonic seizure threshold in the group received a combined dose of 0.1 mg/kg of diazepam and 6000 IU/kg of vitamin D_3, acutely. The results are expressed as Mean ± S.E.M., n = 10 in all groups.

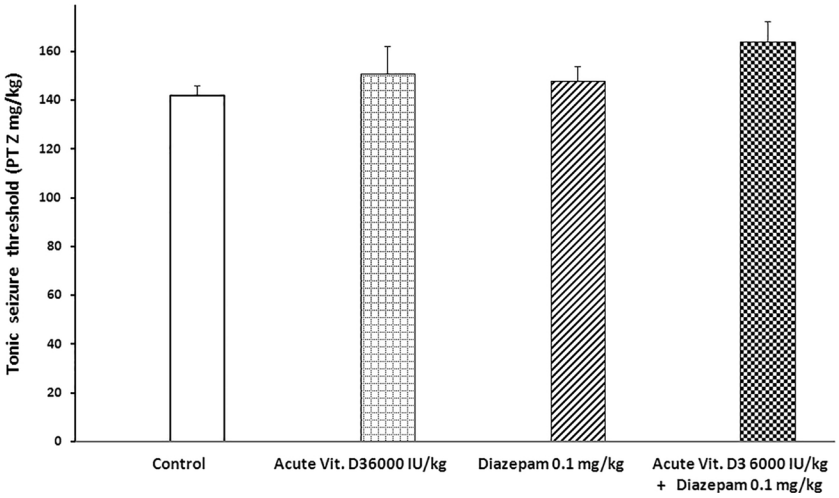

Fig. 8. The mean dose for tonic seizures threshold in the group received combined dose of 0.1 mg/kg of diazepam and 6000 IU/kg of vitamin D_3, acutely. The results are expressed as Mean ± S.E.M., n = 10 in all groups.

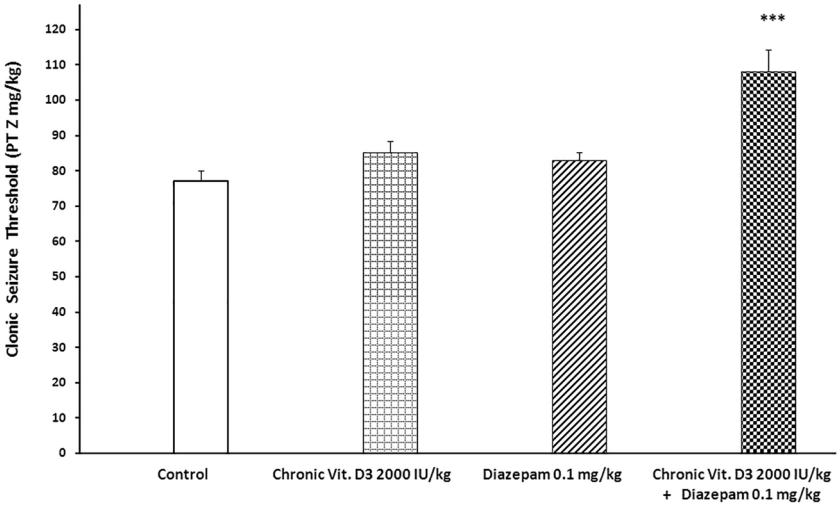

Fig. 9. The mean clonic seizure threshold in the group received vitamin D_3 (2000 IU/kg), diazepam (0.1 mg/kg) and mixture of vitamin D_3 (2000 IU/kg) and diazepam (0.1 mg/kg). The results are expressed as Mean ± S.E.M., n = 10 in all groups. ***P < 0.001 versus control group.

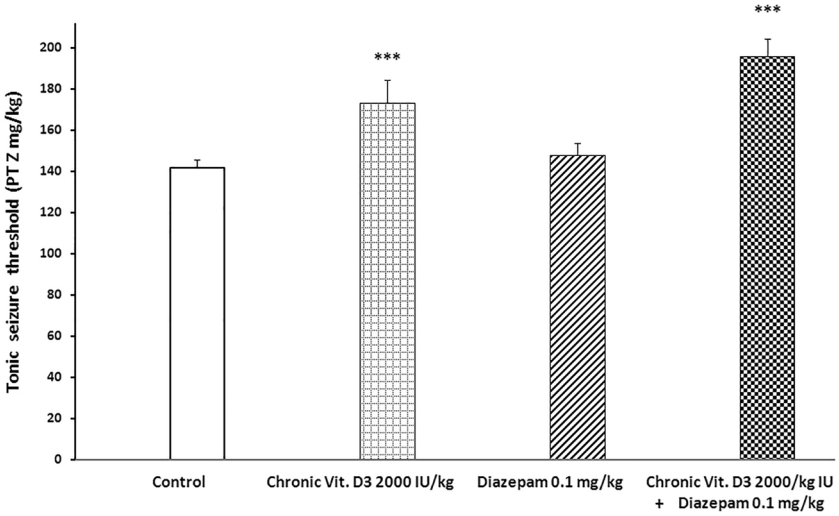

Fig. 10. The mean dose for tonic seizures threshold in the group received vitamin D3 (2000 IU/kg), diazepam (0.1 mg/kg), and mixture of vitamin D3 (2000 IU/kg) and diazepam (0.1 mg/kg). The results are expressed as Mean ± S.E.M., n = 10 in all groups. ** P < 0.01 and *** P < 0.001 versus vehicle.

GABA-A receptors represent an important target for non-genomic action of many neurosteroids such as vitamin D (Neveu et al., 1994) and concerning the crucial role of the GABAergic system in epilepsy pathogenesis, the specific GABA-inhibiting action of PTZ and potentation of diazepam effect with concurrent administration of vitamin D, it is rational to suggest that vitamin D may act through modulation of GABA-A receptors.

Vitamin D could mediate its neuronal effects via modification in transcription of genes encoding a variety of neurotransmitters, enzymes, or cytokines in the nervous system. For example, it has been shown that vitamin D reduces interleukin-6 activity recently reported to be involved in epilepsy and exert pro-convulsant effects in PTZ-induced seizures in rats (Kalueff et al., 2004). Vitamin D also inhibits the synthesis of inducible nitric oxide synthase (iNOS), an enzyme induced in CNS neurons during various insults or diseases. Nitric oxide plays an important role in modulating seizure susceptibility (Garcion et al., 1998). Also, blockade of NOS has been demonstrated to be the anticonvulsant mechanism of action of many compounds such as morphine, dextrometrophan, and tramadol for PTZ-induced seizures in mice (Mohseni et al., 2016). Vitamin D has also been reported to upregulate γ-glutamyl transpeptidase activity and expression of the corresponding gene in rat brain. Because γ-glutamyl transpeptidase is largely involved in the glutathione cycle of the brain in crosstalk between astrocytes and neurons, it has been proposed that vitamin D could control brain detoxification processes. An increase in glutathione levels might be linked to the anti-convulsant effect of vitamin D (Garcion et al., 2002).

Another possible mechanism of vitamin D neuronal effects is the modulation of neuronal Ca^{2+} homeostasis. It was reported that vitamin D down-regulates the L-type voltage-sensitive Ca^{2+} channel in hippocampal neurons, which has been correlated with a neuroprotective effect against excitotoxic insults (Brewer et al., 2001). Given that vitamin D also plays an important role in digestive absorption of calcium, a change in amount of extracellular and intracellular calcium can be considered as a probable mechanism for changing the seizure threshold. Vitamin D deficiency causes hypocalcemia that produces seizure due to increased irritability of the neuron membrane. The anti-seizure activity of vitamin D is probably resulted from its positive effect on mineral homeostasis and hormonal regulation; chronic treatment with anti-seizure medications causes mineral homeostasis disorder in the patients, which increases seizure due to hypocalcemia and a decrease in plasma levels of vitamin D (Teagarden et al., 2014).

5. Conclusions

According to the results of the present study, chronic administration of vitamin D increases the PTZ-induced seizure threshold and the combination of a sub-effective dose of vitamin D_3 and diazepam (0.1 mg/kg), as a typical anticonvulsant drug, can significantly increase seizure threshold. In fact, vitamin D_3 potentiates the anticonvulsant effect of diazepam and vitamin D as a supplement seems to be able to reduce the required dose of anti-seizure medications. Also, due to vitamin D deficiency results from the long-term use of most anti-seizure medications, it is logical to administer vitamin D supplement in patients with refractory epileptic seizures.

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Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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