Thiamine Alleviates Cognitive Impairment and Epileptogenesis by Relieving Brain Inflammation in PTZ-induced Kindling Rat Model

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Abstract

Epileptogenesis, the process by which the brain becomes epileptic, is related to neuroinflammation, hyperexcitability, and as a result cognitive deficits. Evidence suggests that therapeutic strategies targeting pathologic brain inflammation have emerged as a promising approach that prevents or disease-modifying therapy for epileptogenesis. Therefore, the PTZ kindling model of epilepsy was utilized to assess the neuroprotective role of thiamine in epileptogenesis. Male rats were exposed to PTZ-induced kindling and pretreated with low thiamine (25 mg/kg) or high thiamine (50 mg/kg). Cyclooxygenase (COX-1 and COX-2), interleukin 1-beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and nuclear factor-κB (NF-κB) concentrations in the brain were analyzed using biochemical assays. Cognitive function was evaluated using the passive avoidance test. Thiamine ameliorated epileptogenesis and enhanced the rats' performance in the passive avoidance test. Also, thiamine significantly decreased the level of neuroinflammatory mediators in the brain induced by PTZ. These results provide evidence that thiamine alleviates PTZ-induced neuroinflammation and cognitive impairments.

1. Introduction

Epilepsy is a chronic neurological disorder characterized by spontaneous recurrent seizures, which are the result of hyperexcitability and hypersynchrony of brain neurons (Şahin et al. 2019). It is one of the most common diseases of the central nervous system that affect approximately 2% of the world population (do Canto et al. 2021). Antiepileptic drugs (AEDs) are the major treatment for the disease, however, nearly up to 40% of newly diagnosed epilepsy patients fail to respond to these drugs (Bonnett et al. 2017). Moreover, AEDs cannot modulate the underlying pathophysiology, only have seizure suppression. Epileptogenesis, defined as the normal brain becomes epileptic, involves a process that begins after the occurrence of insult and gradually changes neuronal excitability (Castro et al. 2017). This period between the emergence of spontaneous seizures from unprovoked seizures can represent a good opportunity window to change or prevent the progress of the disease. However, there is still no effective treatment that prevents or modifies epileptogenesis. Neuroinflammation has recently been recognized as one of the main etiological factors contributing to epileptogenesis (Alyu and Dikmen 2017). Mounting evidence from animal and human studies indicates that proinflamatuar cytokines and other mediators in the brain play an etiological role in epileptogenesis and the accompanying comorbidity such as cognitive decline (Eastman et al. 2020). The excessive release of these inflammatory mediators can significantly increase the calcium permeability in the glutamatergic neurons causing abnormal neuronal hyperexcitability (Shimada et al. 2014). Therefore, the goal of reducing the levels of neuroinflammatory molecules in the brain points to a potential antiepileptogenic strategy.

Thiamine (vitamin B1) is a water-soluble vitamin that serves as a cofactor for a number of enzymes involved in the energy metabolism and biosynthesis of neurotransmitters (Dhir et al. 2019). Albeit many organs utilize thiamine, the brain is particularly vulnerable to thiamine deficiency related to an impairment of oxidative metabolism, excitotoxicity, brain damage, and inflammation (Hazell and Butterworth 2009). Thiamine deficiency may also be associated with neurological disorders such as Wernicke-Korsakoff

syndrome and neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, all of which are characterized by behavioral, cognitive and neuropathological defects (Inaba et al. 2016; Liu et al. 2017). Remarkably, cases of Wernicke encephalopathy have been reported, which are epileptic seizures that improve after thiamine treatment. (Fu et al. 2017; Shang et al. 2017). It has also been suggested that severe thiamine deficiency may cause epilepsy in infants (Fattal-Valevski et al. 2009a). Moreover, Mesdaghinia et al. showed that chronic treatment with thiamine increases the PTZ-induced tonic and clonic seizure threshold, and suggested that thiamine supplementation in classical AEDs may reduce the required drug doses (Mesdaghinia et al. 2019). Despite the encouraging results regarding the anticonvulsant potential of thiamine, its effect on the epileptic process and the inflammatory response in this process has not yet been the subject of any study. To this end, we aimed to investigate the effect of thiamine pretreatment on epileptogenesis, cognitive function, and brain inflammatory response in the rat PTZ-kindling model.

2. Material And Methods

2.1. Animals

4-5-months-old male Wistar albino rats (230–250 g) were housed in an environment with appropriate temperature (23 ± 2 °C), humidity (35-60%), light (12:12-h light/dark cycle), and free access to food and water. All procedures were performed in accordance with the guidelines of the Local Ethics Committee for the welfare of experimental animals. (65202830-050.04.04-480).

2.2. Experimental design and drug treatments

The experimental design of study illustratively is shown in Fig. 1. Thiamine and pentylenetetrazol (PTZ) were purchased from Sigma-Aldrich (USA) and dissolved in 0.9% saline. All treatments were administered through an intraperitoneal (i.p.). Rats were randomly divided into the following four groups with six rats per group: (i) The control animals were treated with a placebo (physiological saline 1 mL/kg), (ii) PTZ animals were treated with physiological saline (1 mL/kg) 30 min before each PTZ (35 mg/kg) every other day, (iii) TIA-25 animals received thiamine (25 mg/kg) 30 min before each PTZ injection, and (iv) TIA-50 animals received thiamine (50 mg/kg) 30 min before each PTZ injection. To induce kindling in rats, PTZ (35 mg/kg, i.p.) was administered as a repeated subconvulsant dose on each alternate day, as described previously (Taskıran et al. 2020). Following each PTZ injection, the seizure behavior was observed for 30 minutes. The severity of seizure response was scored according to a modified Racine's scale as follows (Lüttjohann et al. 2009): Stage 0: No response, Stage 1: Ear and facial twitching, Stage 2: Head nodding, Stage 3: Myoclonic jerks, Stage 4: Tonic-clonic seizures without loss of postural control, Stage 5: Tonic-clonic seizures with loss of postural control, Stage 6: Tonic-clonic seizures with wild running and jumping, and Stage 7: Lethal seizure. The rats were described as "kindled" when they are obtained a seizure score of 4 for three consecutive days.

2.3. Passive Avoidance Test

This test was performed as described previously (Küçük et al. 2008). The passive avoidance apparatus consisted of a light and dark chamber that was distinguished by an automatically retractable door. The darkroom floor was made from stainless steel grilles. For habitation, rats were slowly placed on the grilled floor, 5 min to adapt to each rat. During the conditioning phase after 24 hours, the rats were placed in the light room, and when the hind legs of both rats entered the dark room, the sliding door was automatically closed. Then, an electric charge at the foot (0.25 mA, 2 s) was supplied by the ground grids. At the end of 10 seconds, the rats returned to their cages. After 24 hours, the delay time required for the rat to enter the darkroom was recorded during the retention test in which the electric shock was removed. The cutoff time for the training and retention session was set at 300 seconds.

2.4. Biochemical analysis

The content of COX-1, COX-2, IL-1β, TNF-α, NF-κB was determined in both hippocampus and cerebral cortex on the 30th day of the end of the experiment. The brain tissues were homogenized in an ice cold phosphate buffer solution (pH: 7.4) through a hand homogenizer. These homogenates were centrifuged at 4000 rpm for 10 min at 4 °C. The supernatant of the centrifuged homogenate was removed and the protein content was measured using the Bradford protein assay (Ernst and Zor 2010). The brain cytokine levels were measured by using enzyme-linked immunosorbent assay (ELISA) kits in accordance with the instructions given by the manufacturer (YL Biont, Chine). Briefly, after the standard solution and tissue samples were added to the plate, they were incubated at 37 °C for 60 minutes. After the washing step, the staining solutions were added and the tissue samples were incubated at 37 °C for 15 minutes. Next, after the application of the stop solution, the wells were immediately read using an ELISA reader (Thermo Fisher Scientific, Altrincham, UK) at 450 nm.

2.5. Statistical analysis

The data retrieved from each experiment were averaged and expressed as means ± S.E.M. Two-way ANOVA was applied for analysis drug X time interaction on the seizure stage, whereas one-way ANOVA was used in other experiments. Values of $P < 0.05$ were considered statistically significant. Statistical analysis was performed by IBM SPSS Statistical Software Version 22.0 (IBM, Armonk, NY, USA).

3. Results

3.1. Thiamine suppresses PTZ-induced epileptogenesis in rats

First, we asked whether thiamine pretreatment affects epileptogenesis. In comparison with the PTZ group, the PTZ-induced epileptogenesis effectively was suppressed by thiamine pretreatment (Fig. 2, $P < 0.05$). It was also found that pretreatment with a 50 mg/kg dose of thiamine was much more effective at reducing the development of PTZ-induced epilepsy in rats ($P < 0.05$).

3.2. Thiamine attenuates PTZ-induced learning deficits in rats

We tested thiamine pretreatment against memory deficits caused by PTZ administration using a passive avoidance test. The delay in entering the dark room on the conditioning day (learning session) was not different between the groups (Fig. 3, $P > 0.05$). However, the delay to enter the dark chamber in the retention trial was significantly lower in rats in the PTZ group compared to the control animals ($P < 0.05$). Also, the attenuation in learning deficits of the passive avoidance test was significant in animals in the TIA-25 and TIA-50 groups compared to the PTZ group ($P < 0.05$).

3.3. Thiamine inhibits inflammatory mediators in the brain of rats

We then determined the effect of pretreatment with thiamine during the epileptogenic period on the levels of neuroinflammatory mediators in the brain of rats. Statistical analysis showed that PTZ-induced kindling led to an increase in the level of inflammatory mediators in the cortex and hippocampus of rats, but these increases were largely ameliorated by pretreatment of thiamine. (Fig 4A-D and 5A-E, $P < 0.05$).

As shown in Fig. 4 A and B, compared to the control group, increased levels of cortical and hippocampal COX-1 levels were observed in rats treated with PTZ ($P < 0.05$). Thiamine pretreatment limited these pathological increases in COX-1 levels both in the cortex of rats in the TIA-25 group and in the hippocampus of rats in the TIA-50 group. Similarly, compared to the control group, cortical and hippocampal COX-2 levels were elevated in PTZ-treated rats (Fig. 4C-D, $P < 0.05$). However, COX-2 levels were considerably lower in the cortex and hippocampus of animals receiving thiamine pretreatment (specifically TIA-50) compared to the PTZ group ($P < 0.05$).

As shown in Fig. 5A-B, cortical and hippocampal TNF-α increased in PTZ-treated rats compared to the control group ($P < 0.05$), whereas, pretreatment with thiamine, as with COX-1, suppressed the level of the brain TNF-α depending on its concentration of applied. The results presented in Fig. 5C-F show that pretreatment of thiamine decreased PTZ-induced cortical and hippocampal IL-1β and NF-κB levels. Notably, pretreatment with thiamine at 50 mg/kg dose significantly reduced the level of these mediators in the cortex and hippocampus ($P < 0.05$).

4. Discussion

The presence of brain inflammation in epileptogenesis is well documented, and thus targeting neuroinflammation has emerged as a promising approach to the treatment of epilepsy. In the current study, we provide evidence that thiamine pretreatment during epileptogenesis ameliorates neuroinflammation and attenuates behavioral comorbidities in the PTZ-induced kindling rat model. Thiamine reduced PTZ-induced increase of inflammatory molecules including COX-1, COX-2, TNF-α, IL-1β, and NF-κB levels in the hippocampus and cerebral cortex of rats.

Despite the growing interest in addressing epileptogenesis to prevent or modify the disease completely, there is still no an antiepileptogenic drug. Neuroinflammation is one of the important findings of epilepsy and epileptogenesis, which can lead to abnormal neural connectivity and hyper-excitable neuronal network (Vezzani et al. 2019). Studies on epilepsy using both in vivo and in vitro experiments have

reported that numerous cytokines, enzymes, and other inflammatory mediators involved in epileptogenesis (Meng and Yao 2020). Among them, cyclooxygenases (COX-1 and COX-2) are a rate limiting enzymes that catalyzes the biosynthesis of prostaglandins and thromboxanes, and its upregulation during seizures has been reported in both in-vitro and in-vivo models of epilepsy (Tu and Bazan 2003; Barbalho et al. 2016; kalantaripour et al. 2017). Consistent with these findings, we found that PTZ injections increased the level of COX-1 and COX-2 in both the cortex and hippocampus. In addition, thiamine pretreatment decreased the levels of the two COX enzymes in the rat brain. In consistent with our results, Bozic et al. reported that pretreatment with benfotiamine, a synthetic derivative of thiamine, suppressed COX-2 at both the gene and protein levels in lipopolysaccharide-stimulated murine BV-2 microglia (Bozic et al. 2015). It has been shown that targeting the COX system with selective and non-selective drugs as an approach to interfering with epileptic seizures may be beneficial (Ma et al. 2012; Rojas et al. 2014). Together, these observations suggest that COX enzymes may be a good target for the development of neuroinflammation-targeted therapeutics in the management of epilepsy.

NF-κB is a transcription factor that regulates genes encoding many proinflammatory cytokines such as pro-interleukin1-β (pro-IL-1β), TNF-α, and interleukin-6 (IL-6) (Sanz and Garcia-Gimeno 2020). The NF-κB signaling pathway is involved in a variety of pathological processes associated with neurodegeneration in the CNS, including seizures and epilepsy (Di et al. 2011). Consistent with this, we found that PTZ-induced epileptogenesis caused an increase in brain levels of TNF-α and IL-β as well as NF-κB. Thiamine pretreatment attenuated neuroinflammation as evidenced by the reduction in NF-κB, IL-1β, and TNF-α levels in rat cortical and hippocampal tissues. These results are in line with previous in-vitro studies reporting that thiamine derivatives decreased inflammation by suppressing activation of NF-κB signaling and consequently alleviate the TNF-α transcription (Bozic et al. 2015; Sambon et al. 2020).

Remarkably, thiamine deficiency led to increased concentrations of cytokines such as TNF-α and IL-1β in brain regions including the cortex and hippocampus (Zahr et al. 2014; Toledo Nunes et al. 2019). This suggests that there may be an interaction between thiamine deficiency and seizure formation in an epileptic brain. Supporting this possibility, Fattal-Valevski et al. have reported that severe deficiency of infants' thiamine may cause epilepsy (Fattal-Valevski et al., 2009). Moreover, it has been suggested that increased seizure sensitivity caused by lead poisoning in rats may be mediated by changes in thiamine levels (Hoon Cheong et al. 1999).

Cognitive impairments such as spatial memory deficit frequently manifest in patients with epilepsy (Lenck-Santini and Scott 2015). Consistent with our results, it has been shown in previous studies that PTZ-induced epileptogenesis causes learning and memory impairments (Üzüm et al. 2010; Filiz et al. 2021). Chemical kindling induced by PTZ leads to structural pathological changes, oxidative stress, and neuroinflammation in the hippocampus, which is the essential structure of the brain in learning and memory (Samokhina and Samokhin, 2018; Taşkıran and Taştemur, 2020). Our results also showed that thiamine pretreatment alleviated learning deficits caused by PTZ-kindling. Thiamine is a neuroinflammation modulator known for removing reactive oxidative species (Liu et al. 2017; Taskiran

and Ergul 2021). Also, previous studies reported that benfotiamine can exert antiinflammatory effects (Sánchez-Ramírez et al. 2006; Shoeb and Ramana 2012). Considering the constantly increasing oxidative stress and inflammation in the epileptic hippocampus, it is plausible that the neuroprotective effect of thiamine is likely a result of its potent antiinflammatory effect.

In conclusion, the results of the current study establish that controlling the extent of neuroinflammation with thiamine treatment can abate both epileptogenesis progression and memory deficit. Considering the high cost of acquiring synthetic drugs and the side effects associated with drug administration, we suggest that such vitamins and vitamin products can be used as an adjunct to antiepileptic drug therapies in the management of epileptogenesis and epilepsy. Further studies are needed to address whether thiamine treatment has an effect on other components involved in epileptogenesis, such as multiple molecular changes, decreased neurogenesis, and abnormal synaptic reorganization in the brain.

Declarations

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Conflict of interest: The authors declare that they have no competing interests.

Availability of data and material: All data are available upon request.

Code availability: It is not applicable.

Authors' contributions: Sebahattin Karabulut contributed to the experimental design, statistical analysis, manuscript writing, and editing. Ahmet Kemal Filiz contributed to the experimental design and experimental procedures. Recep Akkaya contributed to the experimental design, biochemical analysis, and manuscript editing.

Ethical approval: The applied procedures and techniques, in the present study, were approved by Sivas Cumhuriyet University Local Ethics Committee, Sivas, Turkey. The approval number is 65202830-050.04.04-480. Handling of the animals was performed according to the international guidelines of laboratory animal care and use.

Consent to participate: It is not applicable.

Consent for publication: The data provided here is original.

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Figures

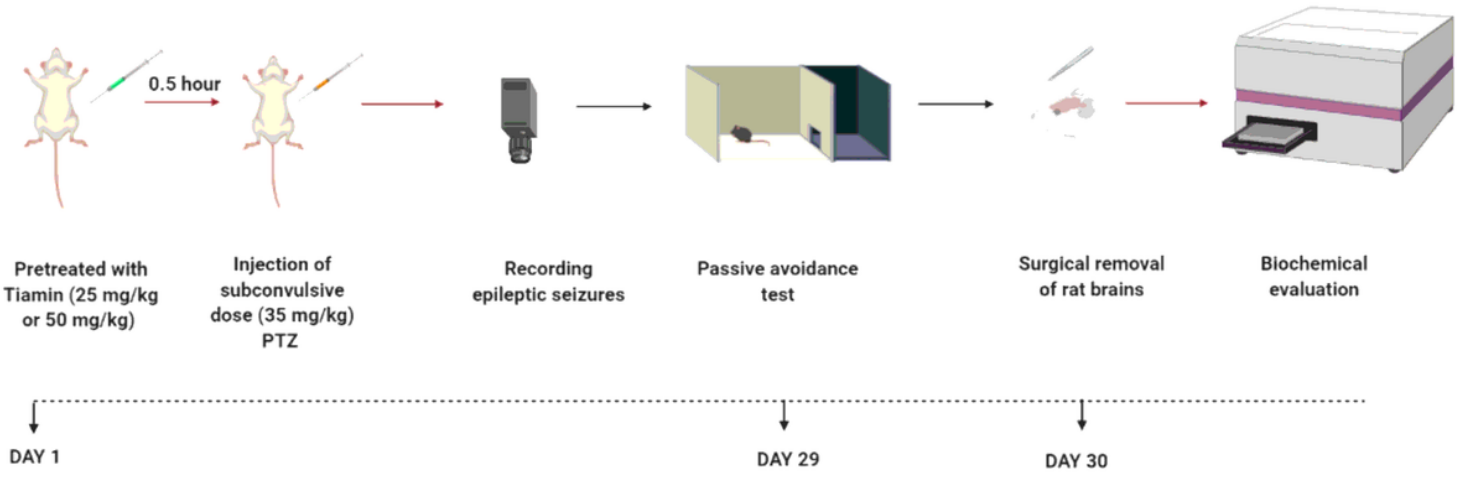

Figure 1

Schematic presentation of the experimental protocol of the study

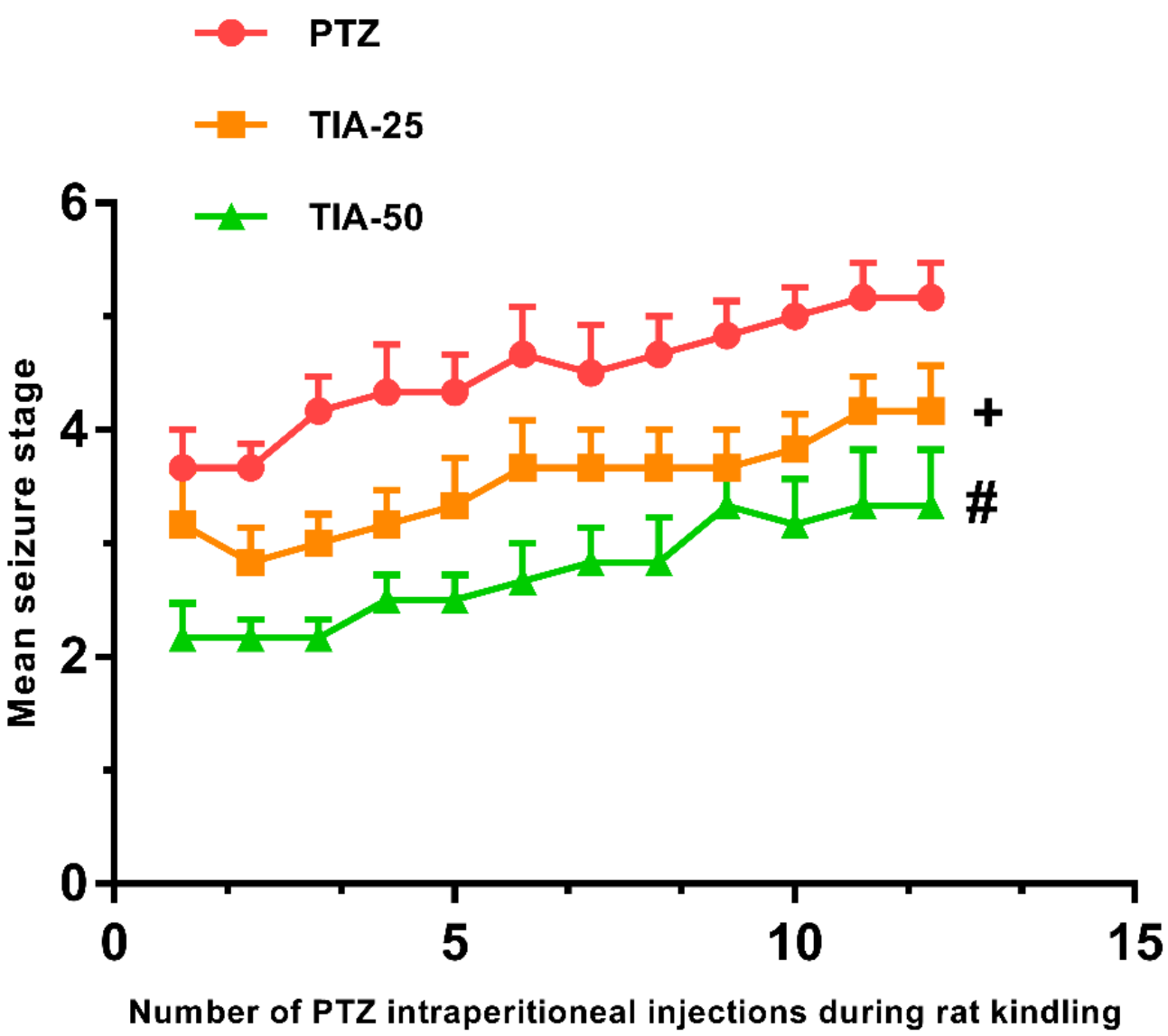

Figure 2

Effect of the pretreatment of thiamine on seizure stage during epileptogenesis process. Values are presented as mean ± SEM. (n =6 rat in each group). +p<0.05 vs PTZ group; #p<0.05 vs TIA-25 group.

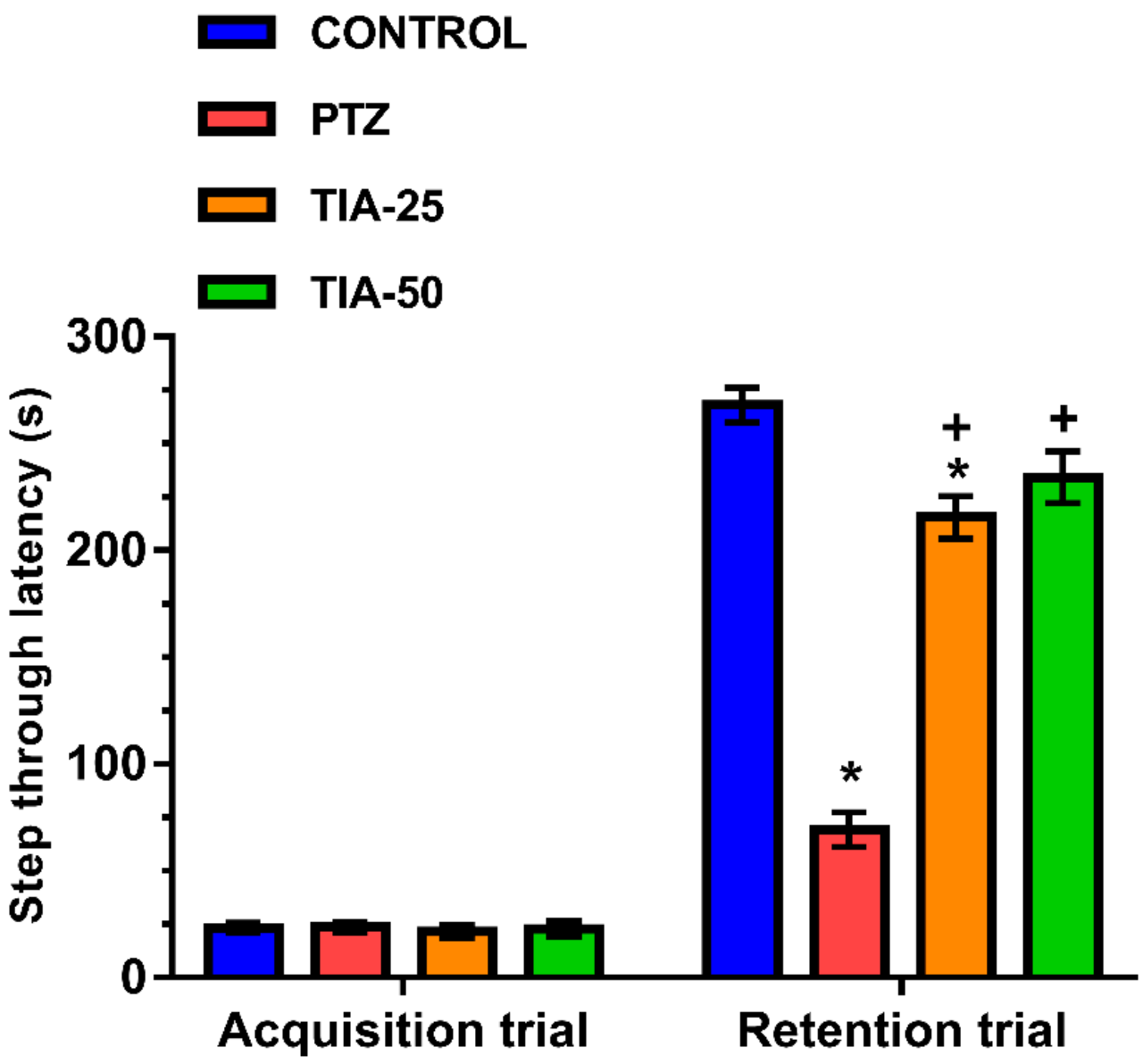

Figure 3

Effect of the pretreatment of thiamine in PTZ-kindled rats on memory performance during the passive avoidance test. Values are presented as mean ± SEM. (n = 6 rat in each group). *p<0.05 vs Control group; +p<0.05 vs PTZ group.

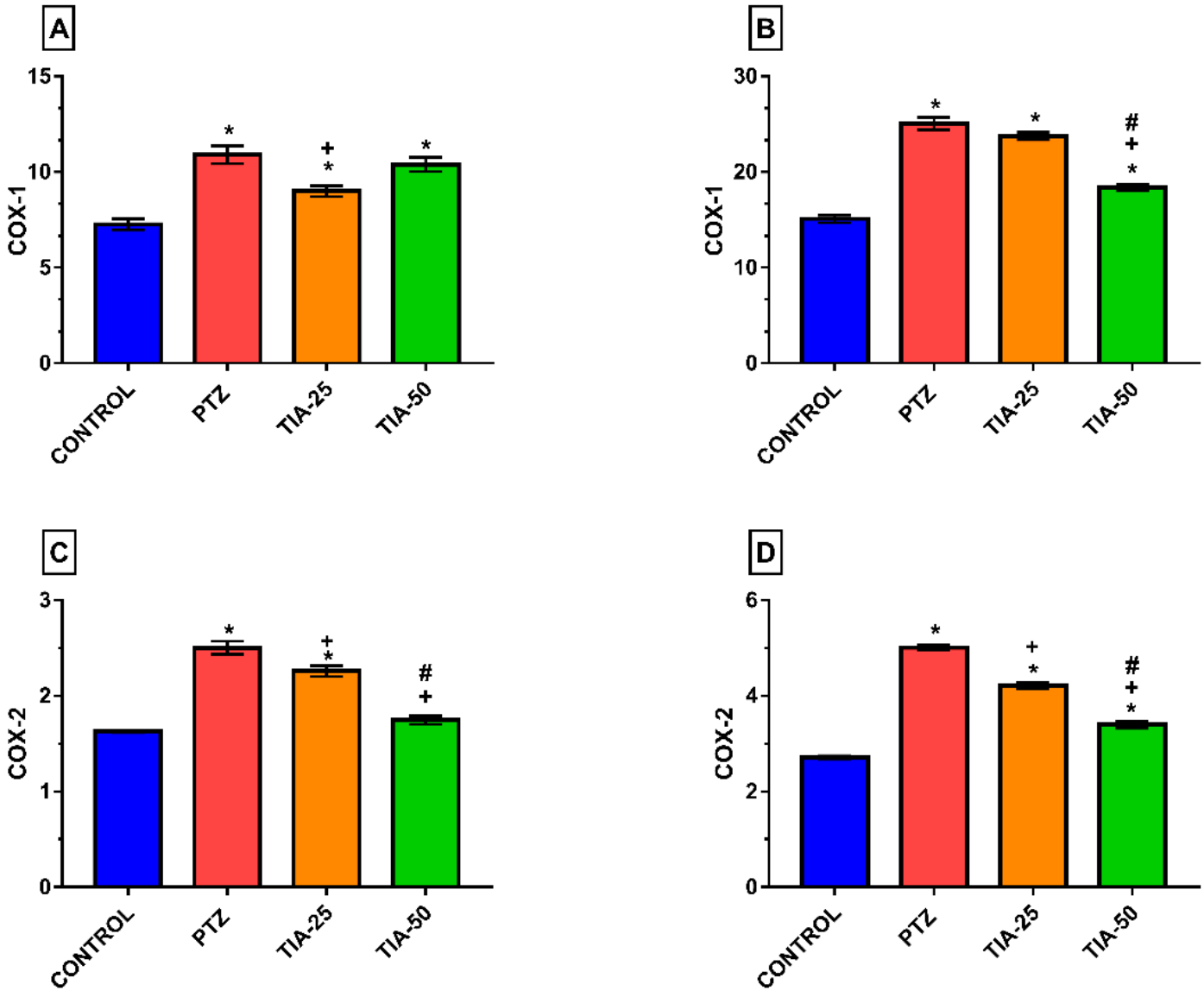

Figure 4

Effect of the thiamine on COX-1 levels in cortex (A) and hippocampus (B); COX-2 levels in cortex (C) and hippocampus (D). Values are presented as mean ± SEM. (n = 6 rat in each group). *p<0.05 vs Control group; +p<0.05 vs PTZ group; #p<0.05 vs TIA-25 group.

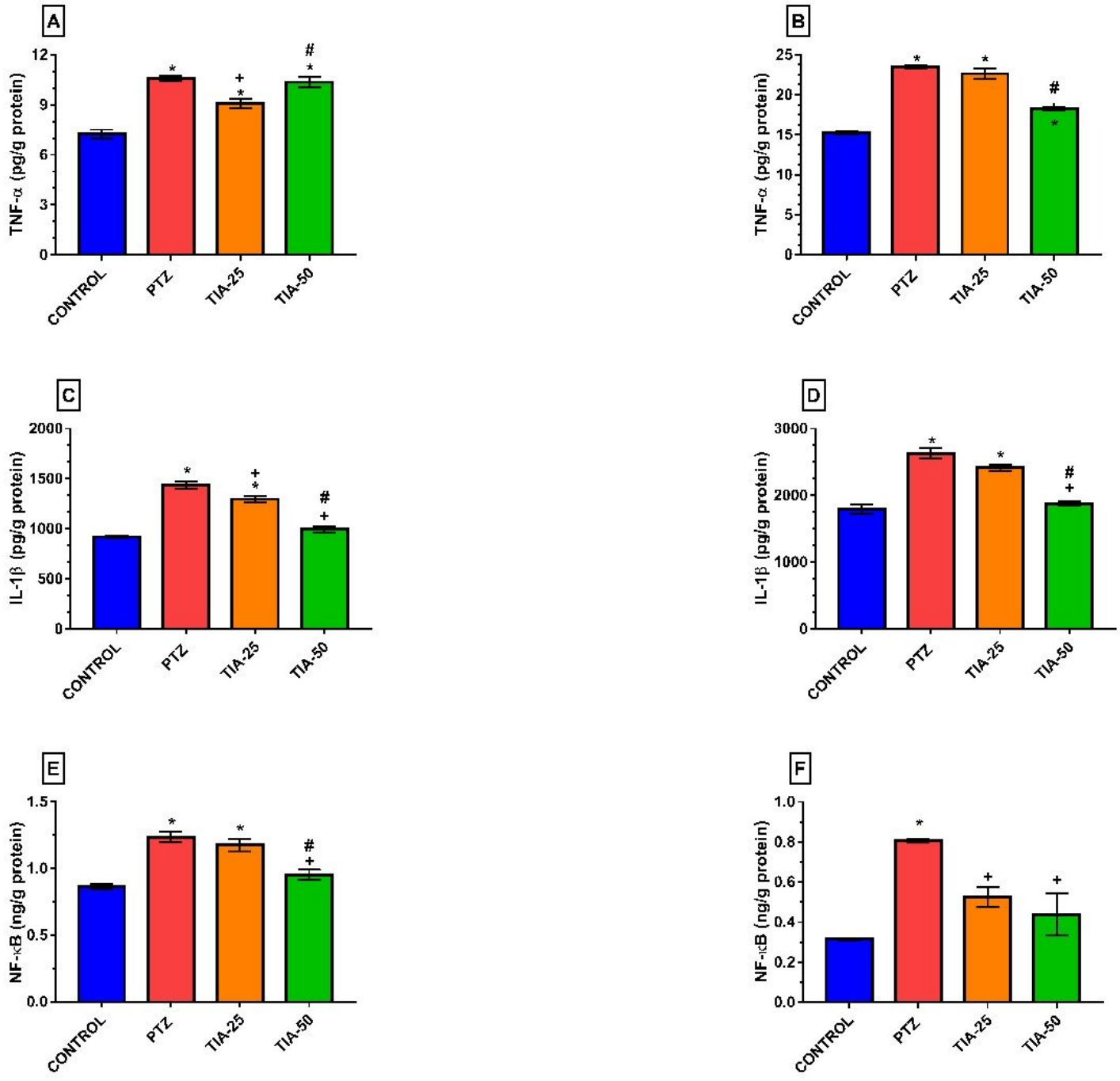

Figure 5

Effect of the thiamine on TNF-α levels in cortex (A) and hippocampus (B); IL-1β levels in cortex (C) and hippocampus (D); NF-κB levels in cortex (E) and hippocampus (F). Values are presented as mean ± SEM. (n = 6 rat in each group). *p<0.05 vs Control group; +p<0.05 vs PTZ group; #p<0.05 vs TIA-25 group.