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Research Article
Effect of Thiamine Pyrophosphate Upon Oxidative Brain Injury Induced by Ischemia-Reperfusion in Rats

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Abstract

Background and Objective: Exposure of the brain to Ischemia-Reperfusion (I/R) may cause tissue damage through oxidative stress. Thiamine pyrophosphate (TPP), which has a protective effect against oxidative stress, is the active metabolite of vitamin B_1. In this study, the protective effect of TPP against possible I/R damage of brain tissue was investigated. **Materials and Methods:** Thirty rats were randomly divided into BIR, TIR and HG groups consisting of ten rats. In the TIR group, 20 mg kg^{-1} TPP was injected intraperitoneally (ip). After 1 hr, clips were placed in the common carotid arteries of the BIR and TIR groups under anesthesia. Brain tissue was subjected to ischemia for 10 min. Afterward, the clips were opened and 3 hrs of reperfusion was achieved. In the HG group, only subcutaneous incisions were made and closed. Then, the brain tissues removed by euthanasia were biochemically analyzed. **Results:** While, I/R increased malondialdehyde (MDA), myeloperoxidase (MPO), Tumor Necrosis Factor-α (TNF-α), Interleukin-1β (IL-1β) and 8-Hydroxyguanine (8-OHGua) levels in brain tissues, total caused a decrease in glutathione (tGSH), glutathione peroxidase (GPO) and glutathione reductase (GSHRd) levels ($p<0.001$). The TPP applied before I/R significantly prevented these changes ($p<0.05$). **Conclusion:** The results of biochemical tests suggested that TPP may be beneficial in preventing possible brain damage due to I/R.

Key words: Anti-inflammatory, antioxidant, ischemia-reperfusion, oxidant, thiamin pyrophosphate, tumor necrosis factors, vitamin B_1

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Ischemia is oxygen deprivation of the tissues and organs as a result of reduced or complete cessation of blood flow to tissues or organs. Brain tissue ischemia results in acute ischemic stroke[1]. Previous studies have suggested that tissue necrosis and irreversible damage develop in ongoing ischemia[2]. Therefore, it is necessary to restore blood flow to ischemia tissue. However, molecular oxygen delivered to the ischemia tissue with large amounts of arterial blood during reperfusion causes excessive production of free oxygen radicals (ROS) in the tissue[3]. This has been known as Ischemia-Reperfusion (I/R) injury. ROS and proinflammatory cytokines secreted from polymorphonuclear leukocytes (PMNL) during I/R cause further exacerbation of tissue damage[4]. Excessive production of ROS and insufficient antioxidant defense mechanisms cause lipid peroxidation and oxidative damage to DNA[5]. The 8-Hydroxyguanine (8-OHGua) is the oxidative damage product of DNA and is a remarkable parameter for determining oxidative stress[5,6]. Understanding the biochemical mechanism of I/R injury, called the oxygen paradox, will help develop new treatment options to prevent tissue damage in clinic[7]. Various methods have been used for determining oxidative stress in cerebral ischemia. In the literature, studies are revealing that total oxidant levels increase in cerebral ischemia models[8]. This information obtained from previous studies shows that oxidant and proinflammatory cytokines play a role in the mechanism of brain damage caused by I/R and this suggested that drugs showing antioxidant and anti-inflammatory activity together may be useful in preventing damage.

In this study, thiamine pyrophosphate (TPP), whose effect was tested against oxidative brain I/R damage, is the active metabolite of thiamine (vitamin B_1)[9]. TPP was the best indicator specifying the activity level of thiamine[10] and formed by the phosphating of thiamine in the liver with thiamine pyrophosphokinase[11]. It has been stated in numerous experimental studies that TPP protected the ovary, peripheral nerve, eye, heart and brain tissue from oxidative stress[11-15]. This information suggests that TPP may protect brain tissue from oxidative I/R damage. In the literature review, no study investigating TPP in brain I/R injury was found. This study was designed to investigate the effect of TPP on I/R-induced brain injury in rats.

MATERIALS AND METHODS

Study area: The current study was carried out at Atatürk University Medical Experimental Application and Research Center in July to August, 2018.

Animals: The experimental animals were procured from Atatürk University Medical Experimental Application and Research Center. For the experiment, a totally 36 months old albino Wistar male rats weighing between 250-265 g were provided. Before the surgical intervention, three groups were created with ten animals in each. The animals were kept for 1 week in an environment with appropriate temperature (21-23°C) and humidity (62-64%), where a 12 hrs light/dark period was automatically provided and their water and feed needs were provided. The procedures were approved by the Experimental Animals Local Ethics Committee (Meeting date: July 26, 2018, Decision no: 8/156).

Chemical substances: The TPP and ketamine were purchased from Biopharma (Russia) and Pfizer (Turkey), respectively.

Experimental animal groups: Three groups were formed using randomization, consisting of ten animals from the rats used in the experiment: BIR, brain I/R applied group, TIR, 20 mg kg^{-1} TPP+brain I/R administered group SG, the control group undergoing the sham operation.

Experiment procedure: All surgical procedures were performed following sterilization rules. The TPP (20 mg kg^{-1}) was injected intraperitoneally (ip) into TIR (n = 10) group 1 hr before anesthesia. Distilled water at the same volume was injected i.p., as the solvent to BIR (n = 10) and SG (n = 10) animal groups. General anesthesia in all animals was administered with 50 mg kg^{-1} ketamine hydrochloride. Surgical interventions were performed while the rats were immobilized in the supine position[16]. During this period, the rats in TIR, BIR and SG groups were kept on the operating table in the supine position. Subsequently, a midline incision was performed shaving and disinfecting the midline of the neck. After superficial microdissection, the right common carotid artery was advanced with deep microdissection. The trachea was reached, the paratracheal muscles were opened to reach the common carotid artery and a clip was placed on the common carotid artery. Ischemia was created by keeping the clips closed for ten minutes. Only subcutaneous incision was performed on the rats in the SG group. Then, the clips were removed, opened incisions were sutured and reperfusion of the brain tissue was provided for 3 hrs. When these processes are completed, the rats were euthanized with 120 mg kg^{-1} ketamine. Malondialdehyde (MDA), myeloperoxidase (MPO), total glutathione (tGSH), glutathione reductase (GSHRd), glutathione peroxidase (GPO), Tumor Necrosis Factor-α (TNF-α), Interleukin-1β (IL-1β) and 8-OHGua levels were measured in the excised brain tissues.

Biochemical analysis

MDA and MPO analysis: The MDA measurements were made according to the method described by Ozer *et al.*[14] The absorbance of the pink complex formed by thiobarbituric acid and MDA was measured spectrophotometrically. For MPO analysis, potassium phosphate buffer (pH = 6) containing 0.5% HDTMAB (0.5% hexadecyltrimethyl ammonium bromide) was prepared from tissue homogenates and centrifuged for 15 min (+4°C, 10000 rpm). The supernatant aliquot was used for analysis. MPO was assayed spectrophotometrically[17].

tGSH, GPO and GSHRd analysis: The tGSH measurement was performed according to the method described by Sedlak and Lindsay[18]. Detection of GPO activity was performed using the method introduced by Lawrence and Burk[1]. Carlberg and Mannervik method was used to determine GSHRd activity. According to this method, the NADPH oxidation rate was measured spectrophotometrically at 340 nm[19].

TNF-α and IL-1β analysis: The tissue homogenate TNF-α (Rat kits, cat no: YHB1098Ra, Shanghai LZ) and IL-1β (rat kits, cat no: YHB0616Ra, Shanghai LZ) concentrations were measured using sandwich enzyme-linked immunosorbent assay. Analyzes were performed according to the manufacturer's instructions.

DNA oxidation analysis: The 8-Hydroxy-2'-Deoxyguanosine (8-OHdG and 8-Hydroxyguanine (8-OHGua) levels were measured on HPLC (HP 1049A ECD Detector, Agilent 1100 modular systems HP 1049A ECD Detector, Germany) with the help of ultraviolet (UV) and electrochemical detectors (ECD). The dG was determined at 245 nm and 8-OHdG was determined by electrochemical reading (600 mV). Sigma brand dG and 8-OHdG standards were used as standards[20].

Statistical analysis: The IBM SPSS Statistics 22.0 program was used to analyze biochemical data. Descriptive statistics results were given as Mean±Standard Deviation (SD). One-way ANOVA was preferred as the statistical analysis method. Tukey test was preferred for group comparisons. Statistical significance level was determined as 0.05. Graphs were made in the GraphPad Prism 9 program.

RESULTS

MDA and MPO analysis results: In Fig. 1a and Table 1, the MDA measurements in the brain tissues of the animals in BIR were found to be high compared to the SG and the TIR groups ($p<0.001$). When MDA levels of the animals in TIR group and SG group with TPP pretreatment were compared, the values were found to be close to each other ($p = 0.407$). Moreover, MPO levels were determined to be higher in the BIR group rather than in SG and TIR groups ($p<0.001$). The TPP brought the MPO levels in the TIR group closer to those in the SG ($p = 0.372$) (Fig. 1b and Table 1).

tGSH, GPO and GSHRd analysis results: The I/R decreased tGSH, GPO and GSHRd levels in BIR when compared to TIR and SG ($p<0.001$). When TIR and SG groups were compared, tGSH and GSHRd values were similar ($p = 0.224$), however, the groups were different for the GPO ($p<0.001$), (Fig. 2a-c and Table 1).

TNF-α and IL-1β analysis results: Whereas, I/R in the brain increased TNF-α and IL-1β levels in the BIR group when compared to the SG ($p<0.001$), this increase was not observed in TIR ($p = 0.658$ and $p = 0.242$, respectively). When TIR and BIR groups were compared, TPP was noticed to decrease TNF-α and IL-1β levels ($p<0.001$) significantly (Fig. 3a-b) and Table 1).

8-OHGua analysis results: The 8-OHGua values obtained from the animals in the BIR group were higher than the ones in SG and TIR groups ($p<0.001$). The TPP administered to the

Table 1: Analysis of biochemical data obtained from study groups

	Group		
Variable	SG (n = 10)	BIR (n = 10)	TIR (n = 10)
MDA (μmol g^{-1} protein)	1.13±0.13	4.60±0.17*	1.33±0.26**
MPO (U g^{-1} protein)	1.65±0.40	5.07±0.73*	2.12±0.57**
tGSH (nmol g^{-1} protein)	6.37±0.42	2.62±0.49*	5.93±0.38**
GPO (U g^{-1} protein)	7.17±0.73	1.80±0.31*	5.53±0.39
GSHRd (U g^{-1} protein)	9.50±0.32	3.18±0.45*	9.03±0.59**
TNF-α (pg L^{-1})	3.77±0.23	13.33±2.16*	4.42±0.38**
IL-1β (ng L^{-1})	2.17±0.48	9.13±0.60*	2.62±0.22**
8-OHGua (pmol L^{-1})	0.69±0.05	1.87±0.18*	0.81±0.08**

*p<0.001 compared to SG and TIR groups, **p>0.05 compared to SG group. Results are shown as Mean±Standard deviation, statistical analysis was done with one-way ANOVA and Tukey HSD was then applied

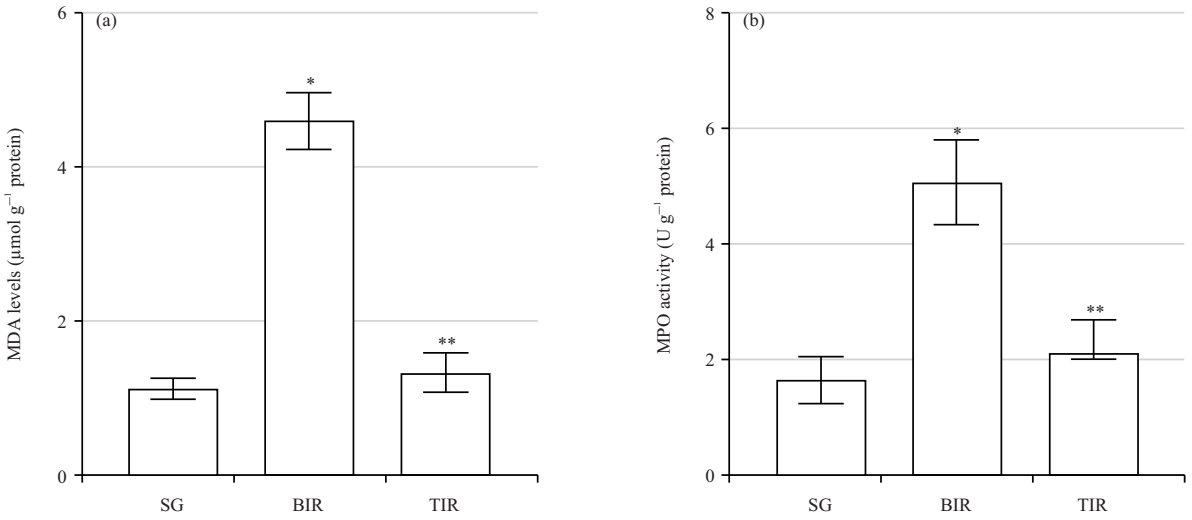

Fig. 1(a-b): (a) MDA and (b) MPO analysis in experimental groups

*p<0.001 compared to SG and TIR groups and **p>0.05 compared to SG group

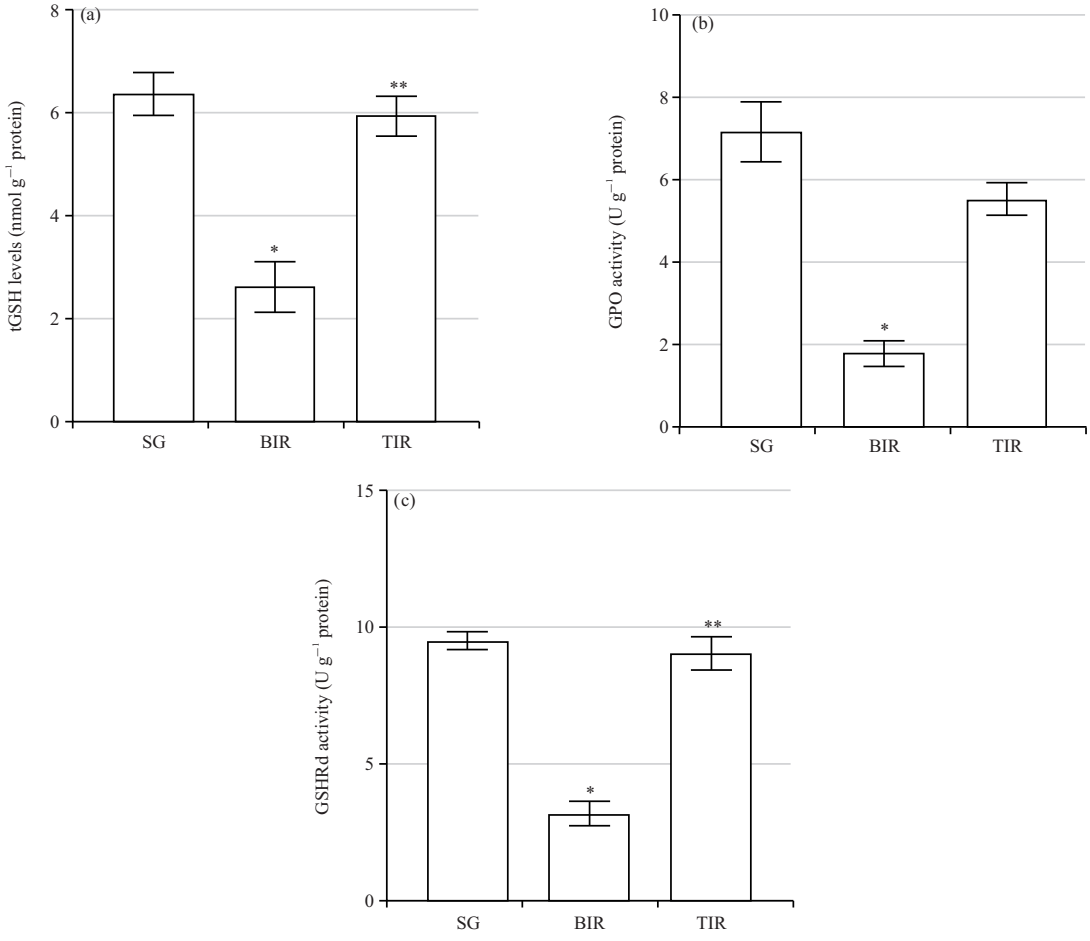

Fig. 2(a-c): (a) tGSH, (b) GPO and (c) GSHRd analysis in experimental groups

*p<0.001 compared to SG and TIR groups and **p>0.05 compared to SG group

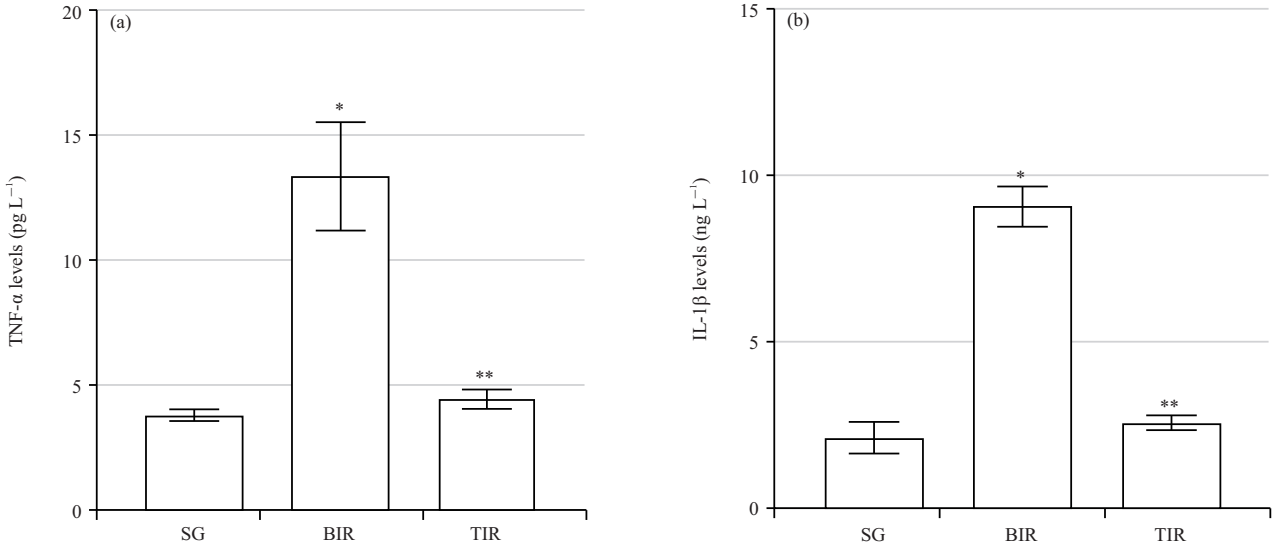

Fig. 3(a-b): (a) TNF-α and (b) IL-1β analysis in experimental groups
*p<0.001 compared to SG and TIR groups and **p>0.05 compared to SG group

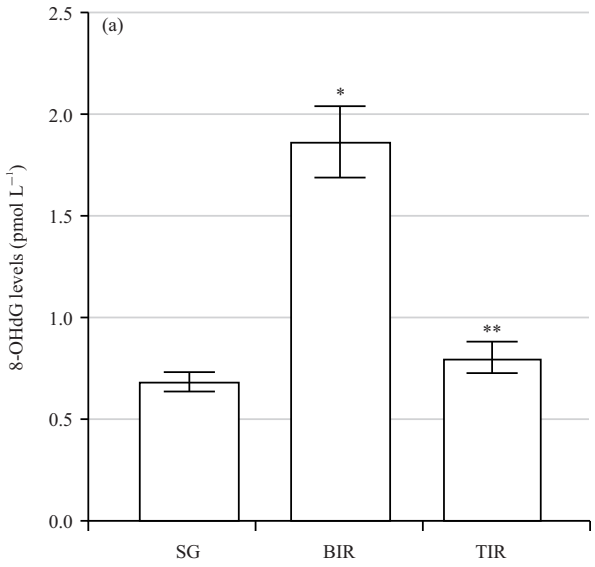

Fig. 4: 8-OHdG analysis in experimental groups
*p<0.001 compared to SG and TIR groups and **p>0.05 compared to SG group

animals in the TIR group prevented this increase and brought 8-OHGua values closer to the ones in the SG (p = 0.200), (Fig. 4 and Table 1).

DISCUSSION

The effect of TPP against the oxidative damage created in the brain with I/R was investigated biochemically. In the study of Cakir *et al.*[21], I/R model was created by placing a clip on the common carotid artery[21]. Our biochemical experiment results revealed that while, I/R increased the levels of oxidant parameters MDA and MPO in brain tissue, it caused a decrease in the levels of antioxidants tGSH, GPO and GSHRd. In addition, it was detected that the expression of TNF-α and IL-1β, which are proinflammatory cytokines and 8-OHdG levels increased depending on I/R. It was determined that the increase in MDA, MPO, TNF-α and IL-1β and 8-OHdG levels was

suppressed with TPP treatment before I/R and the decrease in tGSH, GPO and GSHRd levels was significantly inhibited.

The I/R -induced oxidative stress contributed to morbidity and mortality in various diseases such as organ transplantation, acute coronary syndrome and stroke accompanied by inflammatory responses. While the ischemia process results in hypoxia and tissue dysfunction, tissue damage increases with reperfusion, causing cell death and inflammation[22]. The ROS released by PMNLs that migrated to the tissue during reperfusion also played role in the exacerbation of I/R damage[23]. An important feature of the damage caused by ROS to cells is lipid peroxidation caused by the oxidation of polyunsaturated fatty acids[24,25]. The MDA was a widely accepted biomarker of stress-induced lipid peroxidation[26]. According to current experimental results, MDA levels were determined to be higher in I/R group animals than the ones that underwent sham operation. It was reported in previous studies that MDA levels increased in the brain tissues of rats applied with I/R[1,21].

It was also observed in this study that MPO as the oxidant parameter used to evaluate I/R-induced neurotoxicity increased in the brain tissue[19]. As known, increased MPO activity was reported both in experimental animal models of ischemia and patients with ischemic stroke. MPO-induced Hypochlorous acid (HClO) production catalyzing the reaction of chloride and H_2O_2. The HClO, on the other hand, revealed oxidative activity reacting with lipids, proteins and DNA[27]. Fang *et al.*[28] also found MPO levels to be increased in the brain I/R model they created in rats similar to our study.

The ROS appeared in cells under physiological conditions and were neutralized with antioxidant defense systems[9]. The increase in oxidant levels and decrease in enzymatic and non-enzymatic antioxidants such as GSH, GPO and GSHRd were regarded to be oxidative stress in the literature[25,29]. In this study, tGSH was detected to be low in the brain tissues of I/R group animals with high oxidant parameters. The GSH was a tripeptide including glutamate, cysteine and glycine and was usually found in reduced form in cell[30]. The GSH provided cytoprotection through the conjugation of electrophiles and reduction of ROS[31]. Yuceli *et al.*[32] revealed that antioxidants were depleted in case of oxidative stress and GSH levels decreased in damaged sciatic nerve tissue induced by I/R.

Furthermore, GPO activity in brain tissues was also determined in this study. GPO activity decreased significantly in tissues exposed to ischemia-reperfusion events. As known, GPO detoxified the H_2O_2 radical formed in the cell converting it into water[30,33]. It was determined in a previous study that GPO levels decreased oxidative damage in the brain with I/R[1]. Samarghandian *et al.*[34] also stated that GPO levels decreased in oxidative damage due to stress induced by movement restriction. Current experimental results revealed that GPO levels decreased in the I/R group -similar to the literature.

The GSHRd, another antioxidant we analyzed in this study, is the antioxidant that converts oxidized glutathione to GSH. This reaction was necessary for the maintenance of GSH levels[33]. In a recent experimental study, GSHRd levels in I/R injury in the brain were detected to be lower than in healthy rats[35]. Moreover, it was revealed in the study of Bhatt *et al.*[36] that oxidative stress developed in the brain tissue after tartrazine treatment was associated with a decrease in GSHRd activity. Similar to previous studies, the biochemical results in this study indicated that the GSHRd activity of the animals in the I/R group was low.

Oxidative stress and inflammation were two critical pathological processes of cerebral I/R injury[27]. Inflammatory mediators were reported to be induced in *in vivo* and *in vitro* cerebral I/R models[37]. The TNF-α and IL-1β levels in the brain tissues of rats were also analyzed in our study. The TNF-α and IL-1β are key proinflammatory cytokines and play a role in inflammatory damage in the central nervous system[38,39]. As could be understood from this study, TNF-α and IL-1β levels in brain tissues of the animals treated with I/R were found to be significantly higher than the animals in healthy and TPP groups. It was also determined by Sun *et al.*[40] that TNF-α and IL-1β levels increased with 24 hrs reperfusion following 2 hrs ischemia in the basal ganglia. It was proved in another experimental study that I/R increased TNF-α and IL-1β expression in the cerebral cortex[41]. Relevant studies and our experimental results supported the idea that TNF-α and IL-1β were involved in the inflammatory response of brain I/R injury.

The 8-OHdG we analyzed in our study was a biomarker reflecting both DNA damage and oxidative stress. It is possible for ROS to change the structure of DNA and can cause the formation of altered purine and pyrimidine bases and various DNA damages such as DNA helix breaks[42]. Turan *et al.*[15] found that 8-OHGua levels increased in oxidative brain damage induced by cisplatin. It was determined in a recent clinical study that serum 8-OHGua levels were high in patients with stroke and this increase was associated with the increase in ROS in brain and the oxidative process[43]. Consistent with the literature, determining high levels of 8-OHGua in the I/R group supported the information that ROS caused DNA damage[42].

The TPP, which we evaluated its protective effect against possible brain I/R damage, is an active metabolite of thiamine[44]. In the literature, there were no studies revealing the effect of TPP against I/R -induced brain injury. However, previous studies suggested that TPP protected the brain from

cisplatin-induced oxidative damage[15]. Sabui *et al.*[45] stated that the levels of oxidative damage products as MDA and MPO decreased with TPP. Similar to the information in the literature, no increase in MDA and MPO levels was observed in TPP group and the values were found to be similar to the sham group. As known, TPP was the cofactor of enzymes that played a role in maintaining cell redox synthesizing NADPH and glutathione[44]. It was reported that TPP prevented the decrease of GSH levels in the brain oxidative damage[15]. Yapca *et al.*[46] also stated that TPP prevented the decrease of GSH, GPO and GSHRd levels in rat ovarian tissue with I/R. As could be seen in our findings, tGSH, GPO and GSHRd levels in the TPP group were close to the ones in the healthy group. These results were consistent with the information that TPP had a strong antioxidant potential and ability to restore the impaired balance between ROS production and antioxidant defense[47].

The TPP has been known to have an inhibitory effect on proinflammatory cytokines as well as antioxidant activity[11]. It was revealed by Ucak *et al.*[48] that the TPP treatment prevented the increase of TNF-α and IL-1β in ethanol-induced oxidative optic nerve damage. Supporting the literature, it was observed that TNF-α and IL-1β levels decreased in TPP group when compared to the I/R group and were close to the healthy group. The experimental results in this study similarly revealed that TPP prevented the increase of 8-OHGua levels with I/R. The results of this study were consistent with the results of Altuner *et al.*[49], who stated that TPP reduced 8-OHGua levels in renal I/R injury.

Applications: Clinical studies have shown that thiamine and its derivatives may be beneficial in the treatment of diabetes-related complications[50]. It was found that TPP used in the treatment of diabetic foot gave positive results[51]. Again, in the literature, thiamine treatment was recommended in the treatment of diseases such as chronic heart failure and diabetic cardiomyopathy, regarding the beneficial effect of TPP supplementation[52]. In conditions such as the use of some anticancer drugs and chronic alcoholism, the expression of thiamine pyrophosphokinase is decreased and the conversion of thiamine to TPP is prevented. Thiamine deficiency can occur despite normal thiamine levels[13]. In these cases, it may be advantageous to prefer TPP.

Limitations: It is important to conduct histopathological and molecular studies in the future to better understand the effect and mechanism of TPP in brain I/R. Investigating the effect of TPP upon I/R-induced brain injury histopathologically is remarkable.

CONCLUSION

Current biochemical findings indicated that oxidant and inflammatory parameters increased in the I/R-induced brain tissue damage in rats, whereas antioxidant capacity decreased. It was understood that TPP inhibited the increase of oxidant and inflammatory parameters with I/R and the decrease of antioxidants in rat brain tissue. Current experimental results also suggested that TPP was possible to be efficient in attenuating I/R-induced oxidative and inflammatory brain damage.

SIGNIFICANCE STATEMENT

Brain tissue is very sensitive to ischemia due to its high energy requirement. Short-term oxygen exposure causes severe damage and the reperfusion process increases the damage with the effect of oxidative and inflammatory processes. In this study, an answer was sought to the question of whether brain ischemia reperfusion injury could be prevented or reduced by using thiamine pyrophosphate. It was understood that TPP prevented the increase of oxidant and inflammatory parameters and the decrease of antioxidants in rat brain tissue. The results of this study reveal that thiamine pyrophosphate can be evaluated as a new treatment strategy in ischemia-reperfusion injury that can occur for different reasons.

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