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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

The Effect of Topiramate on Ischemia-Modified Albumin and Prolidase Enzyme Levels in Nitroglycerin-Induced Adolescent Rat Brain Tissue

Topiramatın Nitrogliserinle İndüklenen Adolesan Sıçanların Beyin Dokusunda İskemi Modifiye Albümin ve Prolidaz Enzim Düzeyleri Üzerine Etkisi

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ABSTRACT

Aim: Migraine is a neurological disorder accompanied by episodic headaches that can also occur in children and adolescents. Environmental and genetic factors play a role in the pathogenesis of migraine and the possible contribution of oxidative stress (OS) is debated. Therefore, the present study focused on the possible effect of topiramate (TPM) on the oxidative stress markers ischemia-modified albumin (IMA) and prolidase enzyme activity in nitroglycerin (NTG)-induced brain tissue of adolescent rats.

Material and Method: In this study, 32 male Wistar albino rats aged 6 weeks (adolescence) were used. Rats were divided into four groups with 8 animals in each group. Rats were administered NTG intraperitoneally (i.p.) once daily and topiramate (TPM) orally (p.o.) twice daily. Groups and doses were formed as follows. Group 1: Control group; Group 2: NTG (10 mg/kg) group, Group 3: NTG (10 mg/kg) + TPM (50 mg/kg) group and Group 4: Only TPM (50 mg/kg) group. Animals were sacrificed at the end of the experiment. After the brain tissues were homogenized, IMA and prolidase enzyme activities were measured spectrophotometrically.

Result: IMA and prolidase levels increased in the NTG-treated group and this increase was found to be significant when compared with the control group ($p \leq 0.05$). The combination of NTG+TPM brought IMA and prolidase levels closer to the control group and numerically reduced them compared to the NTG group. Only the TPM group showed a significant decrease compared to the NTG group ($p \leq 0.05$). In addition, IMA and prolidase levels of TPM were close to the control group.

Conclusion: NTG increased IMA and prolidase levels, indicating that it may trigger oxidative stress. TPM partially reversed IMA and prolidase levels. These results may support the hypothesis that TPM may have an antioxidant effect that suppresses OS. Understanding the pharmacodynamic effects of TPM may enable its more effective use as a therapeutic agent.

Keywords: Topiramate, ischemia-modified albumin, prolidase, adolescent rat, oxidative stress, migraine

ÖZ

Amaç: Migren, çocuklarda ve ergenlerde görülebilen epizodik baş ağrısının eşlik ettiği nörolojik bir bozukluktur. Migrenin patogenezinde çevresel ve genetik faktörler rol oynar ve oksidatif stresin (OS) olası katkısı tartışılmaktadır. Bu yüzden sunulan çalışma, nitrogliserin (NTG) ile indüklenen adolesan ratların beyin dokusunda, topiramat'ın (TPM) oksidatif stres belirteçleri olan iskemi modifiye albümin (IMA) ve prolidaz enzim aktivitesi üzerine olası etkisine odaklanmıştır.

Gereç ve Yöntem: Bu çalışmada, Wistar albino ırkı 6 haftalık (adolesan dönem) 32 adet erkek rat kullanıldı. Sıçanlar, her grupta 8 hayvan olacak şekilde dört gruba ayrıldı. Sıçanlara, NTG intraperitoneal (i.p.) günde 1 kez ve topiramat (TPM) oral (p.o.) günde 2 kez olarak uygulandı. Gruplar ve dozlar aşağıdaki gibi oluşturuldu. Group 1: kontrol grubu; Group 2: NTG (10mg/kg) grubu, Group 3: NTG (10 mg/kg) + TPM (50 mg/kg) grubu ve Group 4: Sadece TPM (50 mg/kg) grubu. Hayvanlar deneyin sonunda sakrifiye edildi. Elde edilen beyin dokuları homojenize edildikten sonra, IMA ve prolidaz enzim aktiviteleri spektrofotometrik ölçüldü.

Bulgular: NTG ile tedavi edilen grupta IMA ve prolidaz seviyelerinde artış görülmüş ve bu artış kontrol grubuyla karşılaştırıldığında anlamlı bulunmuştur ($p \leq 0,05$). NTG+TPM kombinasyonu, IMA ve prolidaz seviyelerini kontrol grubuna yaklaştırmış ve NTG grubuna kıyasla sayısal olarak azaltmıştır. Sadece TPM uygulanan grup, NTG grubuna göre anlamlı azalış sergiledi ($p \leq 0.05$). Ayrıca, TPM'nin IMA ve prolidaz düzeyleri kontrol grubuna göre' yakın değerler aldı.

Sonuç: NTG, IMA ve prolidaz seviyelerini artırarak OS'u tetikleyebileceğini göstermiştir. TPM ise kısmende olsa IMA ve prolidaz düzeylerini tersine çevirdi. Bu sonuçlar, TPM'nin OS'u baskılayan antioksidan etkiye sahip olabileceği varsayımını destekleyebilir. TPM'nin farmakodinamik etkilerinin anlaşılması, terapötik bir ajan olarak daha etkili bir şekilde kullanılmasını sağlayabilir.

Anahtar Kelimeler: Topiramat, iskemi modifiye albümin, prolidaz, adolesan rat, oksidatif stres, migren

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INTRODUCTION

Migraine is a neurological disorder affecting millions of children and adolescents globally (1). Migraine is a pathologic condition in which a headache triggered by optical and acoustic stimuli is accompanied by nausea and vomiting. These headaches reduce adolescents' quality of life and productivity at school (2), and they are more prone to anxiety, depression, insomnia, and behavioral disorders (3). Although migraine is common in all populations worldwide, its pathophysiology is not fully understood except for symptomatic treatments. Therefore, researchers have tried various methods to understand the etiology of migraine in experimental animal models (4). One of these methods is the administration of nitroglycerin (NTG) to induce migraine headaches. NTG is a pharmacological agent used to provide a vasodilator effect in blood vessels in cardiovascular diseases such as unstable angina and myocardial infarction (5). However, cluster headaches after NTG use are unwanted side effects. Therefore, NTG is used in in vivo research because it mimics migraine-like headaches. The vasodilating effect of NTG increases the release of exogenous and endogenous nitric oxide (NO) in the endothelium of blood vessels, causing vasodilation in the meningeal vessels of the brain, which can cause migraine headaches. Furthermore, NTG increases NO release, develops tolerance to prolonged use, and causes pro-oxidant effects (6), and NO reacts with peroxynitrite and produces superoxide, a reactive oxygen radical, leading to OS. Thus, it can cause damage to other organs, including brain tissue (6,7). Pharmacologic agents such as topiramate (TPM) and amitriptyline are used to prevent migraine attacks in children and adolescents (8). TPM is a neuromodulating antiepileptic drug and has been suggested to be effective in the prophylactic treatment of migraine by inhibiting sodium and calcium channels and reducing the release of neurotransmitters (9,10). There are studies suggesting that the use of TPM in migraine reduces headaches in adults and children. However, it was emphasized that there are limited studies in children and adolescents and possible side effects should not be ignored (9).

Migraine attacks have been linked to many factors (4). Oxidative stress (OS) is one of these factors. OS is a shift in the oxidant/antioxidant balance in the body in favor of oxidants and has been suggested to contribute to the onset of migraine attacks (11). The excess of polyunsaturated fatty acids in the nervous system and the fact that it is not rich enough in antioxidant enzymes increase the susceptibility of cells to OS (12). OS can lead to increased lipid peroxidation and damage to cell membranes, enzymes, proteins, and DNA (13). Increased oxidant products have been suggested to cause an increase in vasoconstrictors such as angiotensin and urotensin, which are thought to be involved in migraine attacks (14). Recently, ischemic-modified albumin (IMA) and prolidase enzymes have been used as OS markers (15–17). Reactive oxygen species (ROS) disrupt the oxidant/antioxidant balance in the organism during ischemia, leading to changes in the structure and function of albumin. This decreases the capacity of albumin to bind heavy metals such as nickel and cobalt to the N-terminus and leads to an increase in albumin levels. This oxidized albumin molecule is called IMA (17,18). Prolidase is a peptidase found in the cytoplasm of cells that has the unique ability to cleave proline or hydroxyproline at its C-terminal end (19). In addition to plasma, prolidase is also found in organs such as the brain, liver, and heart. Prolidase plays an important role in collagen synthesis by secreting proline, thus maintaining tissue integrity (12,18,20). It is known to affect inflammation, angiogenesis, cancer, and wound healing processes. Furthermore, proline is thought to be a neurotransmitter in the central nervous system and has been reported to be a neuromodulator in synaptic transmission. Increased proline levels affect prolidase enzyme levels and are thought to potentiate the effect of glutamine, which plays a role in the pathogenesis of migraine (18).

Migraine attacks are known to be triggered by many factors and determining the possible contribution of OS to these attacks is one of the topics of current research. To our knowledge, there is no study investigating the effect of TPM on IMA and prolidase enzyme levels, which may be markers of oxidative stress, in adolescent rats. Therefore, the present study focused on the possible effect of TPM used in the treatment of migraine in children and adolescents on IMA and prolidase enzyme activity and its relationship with oxidative stress.

MATERIAL AND METHOD

Animals

In this study, 32 male Wistar albino rats aged 6 weeks (adolescence) were used. All animals were housed under the same physiological conditions, reverse illumination was applied at 12-hour intervals, and standard rat chow and tap water were given ad-libitum in an environment with a room temperature of 20-24°C and 40-60% humidity. This study was approved by the local ethics committee and animal care guidelines were followed (Date:22/06/2023, Number:2023/08-04).

Experimental procedure

The experimental procedure was inspired and modified from previous reports (21–24) The animals were divided into 4 groups and each group consisted of 8 rats. Group 1: Healthy control group; no agent was administered. Group 2: NTG group; NTG (10mg/Kg i.p.) was administered once daily for 5 days. Group 3: NTG+TPM group; NTG (10 mg/Kg, i.p.) (1 time per day) + TPM 50 mg/kg (5 days) (administered orally twice 12 hours apart). Group 4: TPM

50 mg/kg (5 Days) only (administered orally twice 12 hours apart). All subjects were sacrificed under general anesthesia with a 10 mg/Kg dose of xylazine HCl and 75 mg/Kg Ketamine by the bloodless release method. The obtained brain tissue was stored at -80 °C until the time of the study.

Preparation of Homogenate

Samples were homogenized to 20% tissue homogenate with a glass homogenizer in ice molds using phosphate buffer (pH 7.4). Tissue homogenates were taken into pre-labeled tubes and centrifuged at 14000 g for 20 minutes at +4°C. The resulting supernatants were placed in Eppendorf tubes and stored in a deep freezer at -80°C until working (25,26).

IMA Assay

IMA levels were performed by the method reported by Bar O et al (27). Briefly, 200 µL of the supernatant sample was added to 50 µL of 0.1% cobalt chloride and vortexed. This mixture was incubated at room temperature for 10 minutes. Then, 50 µL of Dithiothreitol (DTT) was added to the mixture and incubated for 2 minutes to allow the reaction with cobalt to take place. Then 1 mL of saline solution was added and the reaction of the mixture was stopped. Blinds of the sample were prepared in the same way without the addition of DDT. The absorbance values of the samples were measured spectrophotometrically (T80+ UV-vis spectrometer, United Kingdom) at 470 nm wavelength and IMA levels were calculated.

Prolidase Assay

Prolidase activity was determined using the method proposed by Myara et al. (1982) (28). 100 µl of supernatant was mixed with 100 µl of saline. 25 µl of the mixture was taken and mixed with 75 µl of pre-incubation solution (1 mmol/L GSH, 50 mmol/L MnCl2, 1 mmol/L GSH in 50 mmol/L Tris HCl buffer at pH:7). The mixture was incubated at 37˚C for 30 min. After incubation, 100 µl of a pH 7.8 solution containing Gly-Pro was added and incubated at 37˚C for 5 min. 1 ml of glacial acetic acid was added to the mixture. To the mixture was added 300 µl of tris-HCl buffer at pH: 300 µl of tris-HCl buffer at pH: 7.8 and 1 ml of ninhydrin solution. The tube was capped and kept in a 90˚C water bath for 20 minutes. The mixture was subjected to the ice bath, cooled and absorbances were read at 515 nm without waiting.

Statistical Analysis

The results of the study are shown as Mean and Standard Deviation. One-way Analysis of Variance (ANOVA) was used to compare group means. Following the analysis of variance, the Duncan test was used to determine the different groups. The statistical significance level was taken as 5% and the SPSS (IBM SPSS for Windows, ver.26) statistical package program was used for calculations.

RESULTS

In this study, the changes in IMA and prolidase enzyme activity levels in the brain tissue of adolescent rats treated with NTG and TPM are shown in **Table 1**. When the findings were analyzed in terms of IMA levels, it was observed that the NTG group was significantly higher than the control group ($p \leq 0.05$). IMA levels approached the control with the combined application of NTG+TPM. Only the IMA values of the TPM group were similar to the control group and did not show a significant difference ($p \geq 0.05$). Brain tissue prolidase enzyme level was highest in the NTG group and this value was significant when compared with the control ($p \leq 0.05$). Prolidase levels in the NTG+TPM group decreased numerically compared to the NTG group. However, this decrease was not significant ($p \geq 0.05$). IMA and prolidase levels between the groups are also presented in detail in **Figure 1**.

Table 1: IMA and prolidase levels in NTG and TPM-treated adolescent rats.

Groups	IMA (ABSU) (Mean±SD)	PROLIDASE (U/g tissue) (Mean±SD)
Control (Sham)	0.83 ± 0.36^{b}	3.11 ± 0.38^{c}
NTG (10 mg/kg)	1.24 ± 0.29^{a}	$4.65 \pm 1,08^{a}$
NTG (10 mg/kg)+TPM (50 mg/kg)	1.03 ± 0.18^{ab}	$4.07 \pm 0,62^{ab}$
TPM (50 mg/kg)	0.93 ± 0.08^{b}	$3.45 \pm 0,65^{bc}$

IMA; Ischemic-modified albümin, NTG; Nitroglycerin, TPM; Topiramate, a,b,c p: values with different letters are significant when compared with each other. Data are presented as mean±SD ($p \leq 0.05$).

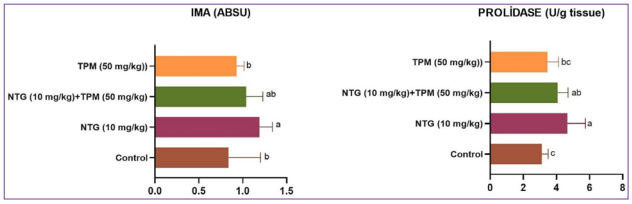

Figure 1. IMA and prolidase levels in adolescent rats. IMA; Ischemic-modified albümin, NTG; Nitroglycerin, TPM; Topiramate, a,b,c p: values with different letters are significant when compared with each other. Data are presented as mean±SD ($p \leq 0.05$).

DISCUSSION

The present study evaluated the effect of TPM on the OS markers IMA and prolidase enzyme activity in NTG-induced adolescent rats. The present study is the first study to investigate oxidative stress indicators (IMA and prolidase) in the brain tissue of adolescent rats in a migraine model based on a literature search. NTG-induced brain tissue increased IMA and prolidase activity, whereas TPM decreased the increased IMA and prolidase levels. The data presented indicated that NTG may induce OS, while TPM may exhibit antioxidant properties.

NTG administration has been reported to have the ability to induce OS (29). Indeed, in one study, NTG increased malondialdehyde, a marker of OS, and decreased

levels of antioxidant enzymes such as glutathione and glutathione peroxidase (21). NTG administration has also been shown to induce OS in rat brain tissue (30) However, there is no study showing the effect of NTG on IMA and prolidase levels, which are markers of OS. In this study, NTG administration induced OS and increased IMA and prolidase levels, consistent with the literature. These results support the hypothesis of a possible contribution of oxidative stress in migraine attacks. Increased IMA levels may cause ischemia-induced increases in reactive oxygen species, hypoxia, acidosis, and damage to cell membranes. This damage is attributed to the decreased ability of albumin to bind heavy metals (such as copper and cobalt) at its N-terminal end (31). IMA has also been reported to be a specific marker for ischemia in the circulatory system (32). However, it is elevated in neoplastic diseases, pulmonary embolism, stroke, and inflammations (31,33,34). There are studies suggesting that IMA level increases in neurological diseases such as migraine (12,18). Say et al. (2020) reported that IMA levels were high in the interictal period in their study (18). From another perspective, migraine patients may develop lesions in the white matter due to ischemia and hypoxia in small vessels in the brain and it has been suggested that this may increase IMA levels (12). In this context, IMA levels may be a marker of OS in neurological disorders. Prolidase activity is an enzyme that functions in all tissues, including the brain, and breaks down dipeptides in proline metabolism. It also plays an important role in collagen synthesis and cell growth (35). There is thought to be a linear relationship between increased prolidase and proline levels (18). Increased levels of proline in the brain have been shown to contribute to neurological disorders by triggering OS (36). N-acetyl aspartate reduction is thought to contribute to the pathophysiology of migraine. It has been reported that this decrease may be linked to OS and mitochondrial dysfunction and may trigger migraine attacks by causing intracellular migration of calcium ions, excessive production of free radicals, and oxidative phosphorylation deficiency (37). Indeed, when NTG was administered to rats, it was associated with oxidative stress as it caused mitochondrial dysfunction (2). Another study reported that NTG administration increased oxidative stress and decreased antioxidants in brain tissue (38). The findings of this study confirm the hypothesis that increased IMA and prolidase levels with NTG administration can be explained by mechanisms similar to the above literature and may be related to oxidative stress.

TPM is a monosaccharide compound. It is used in epilepsy and migraine attacks (34). In addition, TPM has neuroprotective properties with multiple mechanisms of action (39). There are a limited number of studies investigating the effect of TPM on oxidative stress. In one study, it was reported that kainite-induced increased lipid peroxidation (LPO) levels in rats decreased with TPM treatment (40). However, it was reported that TPM doses decreased NO and LPO levels and increased antioxidant enzyme activities such as catalase and superoxide dismutase in pentylenetetrazole (PTZ)-induced nephrotoxicity (41). Furthermore, TPM has been suggested to ameliorate the decreased antioxidant enzyme activity in the frontal cortex and exhibit neuroprotective properties in an experimental cocaine model in rats (42). The findings of the present study show that TPM decreases IMA and prolidase enzyme activities, which are markers of OS. The therapeutic effect of TPM suggests that it may suppress OS through various mechanisms of action such as being a glutamate receptor antagonist and intracellular blockade of calcium ions as reported in the literature. Indeed, NTG has been found to increase glutamate levels via NO and cyclic adenosine monophosphate (6). It has also been found that the increase in proline, a substrate of prolidase enzyme, increases the amount of glutamate in the synaptic pathway and increased glutamate levels may trigger cortical stimulation and cause migraine attacks (18). TPM has also been shown to improve OS parameters and exhibit antioxidant properties (39). The effect of TPM on OS could be attributed to its antagonistic effect on glutamate receptor subtypes, its antioxidant properties, or its ability to reduce IMA and prolidase levels through different mechanisms of action.

CONCLUSION

In the present study, we evaluated the effect of TPM on oxidative stress markers IMA and prolidase enzyme activity in NTG-induced adolescent rats. Results showed that NTG increased IMA and prolidase levels, while TPM restored these levels. In this context, it has been shown that IMA and prolidase enzymes may be markers of OS in neurodegenerative disorders such as migraine. However, it suggests that the antioxidant properties attributed to TPM may suppress OS or may be explained by neuroprotective mechanisms of action. Further, in vivo studies are needed to understand the antioxidant potential and mechanisms of action of TPM.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the local ethics committee and animal care guidelines were followed (Date:22/06/2023, Number:2023/08-04).

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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