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The Effects of Topiramate and Flunarizine on serum Glutamine and neuropeptide Y levels in adolescent Rats with a Migraine model

Efectos del Topiramato y la Flunarizina sobre los niveles séricos de glutamina y neuropéptido en ratas adolescentes con migraña

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ABSTRACT

This study aimed to investigate the effects of topiramate and flunarizine on serum glutamine and neuropeptide Y (NPY) levels in adolescent (6 weeks) rats with a migraine model induced by trinitroglycerin (NTG). For this purpose, 48 Wistar albino male rats in the adolescent stage were used. The rats were divided into 6 groups, each consisting of 8 animals. Group 1 (n=8): Healthy control group; no agent was applied. Group 2 (n=8): Migraine group; NTG (10 mg/kg, IP) was administered once daily. Group 3 (n=8): Migraine + Topiramate group; NTG (10 mg/kg, IP) was administered once daily, and topiramate (50 mg) was administered orally twice a day. Group 4 (n=8): Migraine + Flunarizine group; NTG (10 mg/kg, IP) was administered once daily, and flunarizine (5 mg) was administered orally twice a day. Group 5 (n=8): Topiramate group only; topiramate (50 mg) was administered orally twice a day. Group 6 (n=8): Flunarizine group only; flunarizine (5 mg) was administered orally twice a day. All applications were performed for 5 days. In the migraine-induced group, a significant increase in glutamine and NPY levels was observed compared to the control group. However, in the topiramate and flunarizine groups (grup 5 and 6), no significant differences were detected in these levels compared to the control group. The NTG application was found to be suitable for creating a migraine model, but to observe better clinical findings, an increase in both dose and duration may be necessary. It was concluded that migraine results in brain damage, and as an indicator of damage, both NPY and glutaminase levels may increase. Glutaminase might be slightly more sensitive than NPY in detecting brain damage in migraine, but this sensitivity should be further compared in more experimental studies.

Key words: Migraine; adolescent rats; Topiramate; Flunarizine

RESUMEN

Este estudio se propuso investigar los efectos del topiramato y la flunarizina sobre los niveles séricos de glutamina y neuropéptido Y (NPY) en ratas adolescentes con un modelo de migraña inducida por trinitroglicerina (NTG). Para ello, se utilizaron 48 ratas macho albinas Wistar en fase adolescente. Las ratas se dividieron en 6 grupos, cada uno de los cuales constaba de 8 animales. Grupo 1 (n=8): Grupo de control sano; no se aplicó ningún agente. Grupo 2 (n=8): Grupo migrañoso; se administró NTG (10 mg/kg, IP) una vez al día. Grupo 3 (n=8): Grupo migraña + topiramato; se administró NTG (10 mg/kg, IP) una vez al día y topiramato (50 mg) por vía oral dos veces al día. Grupo 4 (n=8): Grupo de migraña + flunarizina; NTG (10 mg/kg, IP) se administró una vez al día, y flunarizina (5 mg) se administró por vía oral dos veces al día. Grupo 5 (n=8): Grupo de topiramato únicamente; se administró topiramato (50 mg) por vía oral dos veces al día. Grupo 6 (n=8): Sólo grupo de flunarizina; se administró flunarizina (5 mg) por vía oral dos veces al día. Todas las aplicaciones se realizaron durante 5 días. En el grupo inducido por migraña, se observó un aumento significativo de los niveles de glutamina y NPY en comparación con el grupo de control. Sin embargo, en los grupos de topiramato y flunarizina (grupos 5 y 6) no se detectaron diferencias significativas en estos niveles en comparación con el grupo de control. Se comprobó que la aplicación de NTG es adecuada para crear un modelo de migraña, pero para observar mejores resultados clínicos puede ser necesario aumentar tanto la dosis como la duración. Se llegó a la conclusión de que la migraña provoca daños cerebrales y, como indicador de los mismos, pueden aumentar tanto los niveles de NPY como de glutaminasa. La glutaminasa podría ser ligeramente más sensible que el NPY a la hora de detectar daños cerebrales en la migraña, pero esta sensibilidad debería seguir comparándose en más estudios experimentales.

Palabras clave: Migraña; ratas adolescentes; Topiramato; Flunarizina

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INTRODUCTION

Migraine is an episodic headache disorder accompanied by neurological, gastrointestinal, and autonomic changes and is typically associated with symptoms such as nausea, vomiting, and light sensitivity [1]. Pediatric migraine is common in childhood, with a prevalence of 3-10.6%, and is one of the most common types of chronic episodic headaches [2 , 3 , 4].

It is recommended to avoid unnecessary tests in the diagnosis of migraine and to apply appropriate pharmacological treatments. Flunarizine is frequently preferred as an effective prophylactic agent in pediatric cases [5].

It is reported that rats are used as animal species for the migraine model and there are different migraine model methods [6 , 7]. In animal models, nitroglycerin (NTG) is commonly used to investigate migraine attacks. NTG triggers migraine through its vasodilator effect and is administered in rats (*Rattus norvegicus*) at a dose of 10 mg/kg [8 , 9] Adolescent rats are considered a suitable model representing childhood and adolescence in humans [6 , 7 , 10].

Glutamine and neuropeptide Y (NPY) are significant biomarkers in the pathophysiology of migraine. Elevated plasma glutamate levels in migraine patients, which decrease following prophylactic treatment, have been reported [11]. Oxidative agents are reported to activate Transient Receptor Potential (TRP) ion channels, triggering migraine attacks [12].

This study investigates the effects of Topiramate and Flunarizine on serum glutamine and NPY levels in a migraine model created in adolescent rats. The aim of the study was to test the effects of Flunarizine and Topiramate on the symptoms and some pathophysiological processes of NTG-induced migraine in adolescent rats.

MATERIALS AND METHODS

This study was conducted with ethical approval from the Local Ethics Committee for Animal Experiments of Van Yüzüncü Yil University (decision date: 01.12.2022, number: 2022/12-16). Experimental procedures were carried out at the Experimental Medicine Application and Research Center of Van Yüzüncü Yil University.

Experimental animals and housing conditions

The study used 48 Wistar albino rats, aged 6 weeks (adolescent period). The animals were housed in a room with a 12-hour light/dark cycle, temperature of 20-24°C, and humidity of 40-60%. They were fed standard rat chow and tap water ad libitum.

Groups and treatments

Rats were randomly divided into 6 groups, with 8 animals per group:

Healthy control group (n=8): No procedure was applied.

Migraine group (n=8): NTG (10 mg/kg) was administered intraperitoneally once a day (d) for 5 d.

Migraine + Topiramate group (n=8): NTG (10 mg/kg) was administered once a d, and Topiramate (50 mg/kg) was administered orally twice a d, 12 hours (h) apart, for 5 d.

Migraine + Flunarizine group (n=8): NTG (10 mg/kg) was administered once a d, and Flunarizine (5 mg/kg) was administered orally twice a d, 12 h apart, for 5 d.

Topiramate Only group (n=8): Topiramate (50 mg/kg) was administered orally twice a d, 12 h apart, for 5 d.

Flunarizine only group (n=8): Flunarizine (5 mg/kg) was administered orally twice a d, 12 h apart, for 5 d.

Euthanasia and sample collection

At the end of the experiment, all animals were euthanized under general anesthesia using 10 mg/kg Xylazine HCl and 75 mg/kg Ketamine, followed by exsanguination. Plasma and serum were separated from the blood samples (Nuve®, NF 1200, Türkiye).

Serum analyses

NPY levels: Measured using the species-specific Rat Neuropeptide Y ELISA test (Cat. No: SL0521Ra; Sunlong Biotech Co. Ltd.®).

Glutaminase levels: Determined using the Rat Glutaminase ELISA test (Cat. No: NE010201603; Nephentine®).

Histopathological analysis

Brain tissue samples were fixed in 10% formalin and embedded in paraffin after routine histological processing. Sections of 5 µm thickness were stained with hematoxylin-eosin (H&E) and examined under a light microscope (E-400; Nikon, Japan). Images were recorded with a DS-Ri2 video camera (DS-U3; Nikon, Japan).

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 AND DISCUSSION

A migraine attack is characterized by neuronal and vascular changes involving cortical exitability and the trigeminovascular system. The pathophysiology of migraine has not yet been fully elucidated. Depression, which involves neuronal, glial and

vascular cells, has been reported to affect the cerebral cortex in migraine symptoms. Glial cells play a key role in the alteration of cortical exitability in migraine. Glial cells are critical for central nervous system homeostasis under both physiological and pathological conditions. These cells may play a role in the development and progression of neurological diseases [14 , 15 , 16 , 17].

The general clinical condition of the rats in all groups was good and no significant difference was observed between the groups. It is stated that after the application of NTG in the migraine model, they showed signs of head scratching and tail lifting [18]. During the study, increased head scratching and cage climbing behavior, temporary tension and tail lifting behaviors were observed in the migraine-induced groups following the application of NTG (10 mg/kg). This situation is consistent with the researchers' statements that it occurs because of the migraine model [7 , 13 , 18]. They state that these behaviors disappeared over time and no significant difference was detected in food and water consumption compared to the control group.

Several studies using magnetization transfer ratio (MTR) imaging in migraine patients have reported focal microstructural damage associated with migraine; (another study reported no significant difference in MTR in the whole brain and normal-appearing white matter in migraine patients compared to control subjects. Ischemic microvascular disorders together with focal hypoperfusion of the cerebral parenchyma are known to cause white matter lesions (WMLs) The pathophysiological mechanism leading to the formation of WMLs in migraine and the histopathological effect of migraine-related WMLs are not fully understood [19 , 20 , 21 , 22].

Necrotic neurons and hyperemia were observed in all groups except the control group (FIG. A), but these findings did not show a significant difference between the groups. In the migraine group, glial nodules, necrotic neurons, hyperemic vessels and inflammatory cells were observed in the brain parenchyma (FIGS. 1B-C-D). Glial nodules were not observed in the topiramate group, but hyperemic vessels were evident (FIG. 1G). Glial nodules were not detected in the flunarizine group and histopathological findings were generally normal (FIG. 1H). These findings prove that NTG causes histopathological changes, and the migraine model occurs as stated by the researchers [7 , 18 , 19]. Glial nodules were detected in only one rat in the Migraine + Topiramate Group (FIG. 1E). No pathological changes were observed in the other members of the group. A similar situation was also present in the Migraine + Flunarizine Group (FIG. 1F). No nodules were detected in the Topiramate Only Group, but intensely hyperemic vessels were noted (FIG. 1G). No structural changes were observed in the Flunarizine Only Group and histopathological findings were normal (FIG. 1H). In the light of these histopathological findings, it is thought that this is due to the effectiveness of Topiramate and Flunarizine drugs used in migraine treatment [23 , 24 , 25].

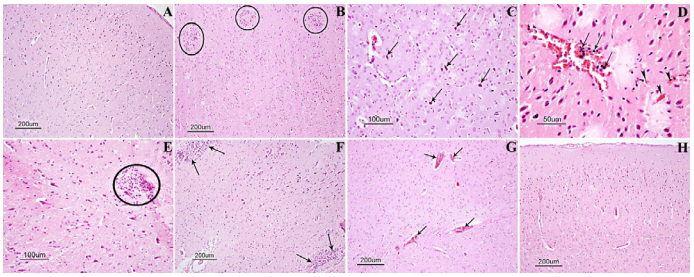

FIGURE 1. Photomicrographs of rat brain sections stained by hematoxylin and eosin staining (H&E.). **A)** Control group; The normal histological structure of the brain tissue is observed. **B)** Migraine group; Glial nodules are observed in the brain. **C)** Migraine group; Necrotic neurons are observed in the brain. **D)** Migraine group; Hyperemia in brain tissue, inflammatory cells (arrows), and free erythrocytes in the brain parenchyma (arrowheads). **E)** Migraine + Topiramate group; Glial nodule structure observed in brain tissue. **F)** Migraine + Flunarizine group; Presence of glial nodules observed in brain tissue (arrows). **G)** Topiramate group; Hyperemia observed in brain tissue (arrows). **H)** Flunarizine group; Histological structure of brain tissue is close to normal.

The decrease in glial nodules and the loss of necrotic neurons support the effectiveness of the treatment protocols used. These findings suggest that both drugs have neuroprotective effects in reducing migraine-induced brain tissue damage. Hyperemic vascular structure was observed in only one animal in the Topiramate only Group, while there was no structural change in the Flunarizine only Group; It shows that Flunarizine and Topiramate drugs work with different mechanisms as stated by the researchers [24 , 25], and that the use of these drugs in therapeutic doses does not cause serious histopathological damage.

Biochemical findings

In this study, the effects of Topiramate and Flunarizine on serum Glutaminase and neuropeptide Y (NPY) levels were evaluated in rats with a migraine model induced by nitroglycerin (NTG). During the study, transient tension and tail-raising behaviors were observed following NTG (10 mg/kg) administration in the migraine groups, which gradually disappeared over time. This observation is considered an indicator that NTG successfully induces migraine attacks. Similarly, Sufka *et al.* [13] reported increased locomotor activity in the NTG-treated group, supporting the validity of the migraine model.

Neuropeptide Y (NPY) is a molecule that acts as a neuromodulator in the nervous system and regulates various functions such as pain, stress, feeding, and blood pressure [26]. In this study, although numerical differences in NPY levels were observed among the groups, these differences were not statistically significant compared to the control group (P>0.05) (TABLE I). In their experimental migraine model study, Guo et al (2021) found that NPY mRNA expression and plasma NPY levels in rats with migraine were significantly higher than the control group [27].

TABLE I
Neuropeptide Y and Glutaminase Levels.

Groups	Neuropeptide Y (pg/mL)	Glutaminase (ng/mL)
Control	40.79 ± 13.13[a]	1.41 ± 0.87[a]
Migraine	57.63 ± 15.84[a]	4.10 ± 1.32[b]
Migraine + Topiramate	43.57 ± 9.40[a]	1.74 ± 1.09[a]
Migraine + Flunarizine	49.85 ± 9.60[a]	1.69 ± 1.77[a]
Topiramate only	48.94 ± 13.73[a]	1.93 ± 0.87[a]
Flunarizine only	47.96 ± 11.72[a]	1.93 ± 0.87[a]
P Value	P>0.05	P>0.05

No statistically significant difference was found when the control and treatment groups were compared as a result of NPY analysis (P>0.05). Glutaminase analysis showed a statistically significant increase in glutaminase levels in the migraine group (NTG) compared to the control and other groups (P<0.05)

These findings suggest that NPY is secreted during migraine attacks and that topiramate and flunarizine, used in migraine treatment, exhibit therapeutic effects. Considering NPY's role in stress, pain, and neuronal excitability, its role in migraine pathophysiology warrants further detailed investigation [28 , 29].

Glutaminase is an enzyme considered a marker of brain tissue damage. Ferrari *et al.* [11] reported significantly elevated plasma glutamate levels in migraine patients compared to control groups. In this study, Glutaminase levels in the migraine group (4.10 ± 1.32 ng/mL) were significantly higher than in the control group (1.41 ± 0.87 ng/mL) (P<0.05), confirming the successful establishment of the migraine model (TABLE I).

The lower Glutaminase levels observed in the Topiramate and Flunarizine groups compared to the migraine group suggest that these drugs suppress Glutaminase levels and demonstrate their therapeutic effects on migraine. These findings suggest that, as researchers [23 , 24 , 25] have different mechanisms and that these drugs may have migraine related neuroinflammation reducing effects.

CONCLUSION

The nitroglycerin (NTG) administration at a dose of 10 mg/kg is suitable for establishing a migraine model. However, increasing the dose and duration could provide more pronounced clinical and histopathological findings. Elevated levels of NPY and glutaminase were observed during migraine induction. However, As a result of the statistical analysis, it was seen that glutaminase may be more sensitive than NPY as a marker of brain damage. This sensitivity requires further validation through more extensive experimental studies. Both Topiramate and Flunarizine showed positive effects on biochemical parameters (NPY and glutaminase) and histopathological findings. This indicates that both drugs may be effective in migraine treatment. While the results of this study provide important information about the pathophysiology of migraine, long-term studies with more comprehensive analyses on the migraine model are needed.

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Conflict of interest

The authors declare that they have no competing financial interests.

Project information

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