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THE EFFECTS OF TOPIRAMATE APPLIED TO THE NUCLEUS ACCUMBENS REGION ON MORPHINE WITHDRAWAL SYNDROME

Nukleus Akumbens Bölgesine Uygulanan Topiramatın Morfin Yoksunluk Sendromuna Etkileri

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Abstract

Aim: Nucleus accumbens, one of the nuclei of the basal ganglia, and dopamine, the neurotransmitter play a critical role in opioid dependence and withdrawal. In opioid withdrawal, the importance of neurotransmitters such as glutamate and gamma aminobutyric acid (GABA), as well as dopamine, is known. In this study, we aimed to investigate the effects of local injections of topiramate, an antiepileptic agent affecting GABAergic and glutamatergic pathways, into the nucleus accumbens on withdrawal signs and locomotor activity during naloxone-induced withdrawal in morphine-dependent rats.

Materials and Methods: Twenty male Sprague-Dawley rats were divided in topiramate treatment and control groups. All animals received morphine pellets and guide cannulas were placed bilaterally in the nucleus accumbens regions by stereotaxic surgery. On the last day of the experiment, following the bilateral topiramate or saline (control group) microinjections, morphine withdrawal was triggered by naloxone.

Results: Topiramate microinjections into the nucleus accumbens region significantly suppressed the signs of naloxone-induced morphine withdrawal such as number of jumpings and weight loss. No significant difference was observed in wet dog shakes, one of the withdrawal signs, after local topiramate treatment. Although topiramate microinjections increased stereotypical activity it did not change locomotor activity behavior such as vertical and ambulatory activity, and total covered distance.

Conclusion: These findings show that local microinjection of topiramate into the nucleus accumbens is effective in preventing opioid deprivation symptoms without significant effect on locomotor activity.

Keywords: Morphine, nucleus accumbens, withdrawal, topiramate.

Öz

Amaç: Bazal gangliyon çekirdeklerinden biri olan nukleus akumbens ve nörotransmitter olan dopamin opioid bağımlılığı ve yoksunluğunda kritik rol oynamaktadır. Opioid yoksunluğunda dopaminin yanı sıra glutamat ve GABA gibi nörotransmitterlerin de önemi bilinmektedir. Biz bu çalışmada morfin bağımlılığı oluşturulan hayvanlarda GABAerjik ve glutamaterjik yolakları etkileyen antiepileptik ajan olan topiramatın nukleus akumbens bölgesine lokal uygulamasının naloksonla tetiklenen yoksunluk sendromunda yoksunluk bulguları ve lokomotor aktivite üzerine etkilerini araştırmayı amaçladık.

Materyal ve Metot: Yirmi adet erkek Sprague-Dawley sıçanları topiramat tedavi grubu ve kontrol grubu olarak ikiye ayrıldı. Hayvanların hepsine morfin peletleri uygulandı, stereotaksik cerrahi işlemle nukleus akumbens bölgelerine kılavuz kanüller bilateral yerleştirildi. Deneyin son gününde bilateral topiramat veya serum fizyolojik (kontrol grubu) mikroenjeksiyonlarını takiben nalokson uygulanarak morfin yoksunluğu tetiklendi.

Bulgular: Nukleus akumbens bölgesine lokal uygulanan topiramat naloksonla tetiklenen morfin yoksunluk bulgularından sıçrama sayısını ve ağırlık kaybını anlamlı düzeyde baskıladı. Lokal topiramat uygulaması yoksunluk bulgularından ıslak köpek silkinmesinde ise anlamlı değişiklik yapmadı. Topiramat mikroenjeksiyonları stereotipik hareketleri artırdığı halde vertikal hareketler, ambulatuvar hareketler ve toplam kat edilen mesafe gibi lokomotor aktivite davranışlarını değiştirmedi.

Sonuç: Bu bulgular antikonvülzan ilaç olan topiramatın nukleus akumbens bölgesine lokal uygulanmasının lokomotor aktivitede anlamlı baskılanma yapmadan opioid yoksunluk belirtilerinin önlenmesinde etkili olduğunu göstermektedir.

Anahtar Kelimeler: Morfin, nukleus akumbens, yoksunluk, topiramat.

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INTRODUCTION

Morphine is one of the opioid alkaloids, obtained from *Papaver somniferum L.* and used to treat severe pain. It mediates effects such as euphoria, sedation, respiratory depression, and slowing of gastrointestinal tract motility, as well as analgesic effect by binding to classical opioid receptors (μ, δ, and κ) that are widely distributed in peripheral tissue and the central nervous system (CNS)[1]. The use of chronic morphine and other opioids causes addiction and withdrawal when exposure is stopped. The mesocorticolimbic dopaminergic system, which extends from the ventral tegmental area (VTA) to the nucleus accumbens (NAc), plays an important role in the addiction and withdrawal mechanism of opioids[2]. In opioid use, the dopamine level increases in the NAc region and remains high as long as the exposure continues[3]. In opioid withdrawal syndrome, increased dopamine levels in the NAc region decreases and withdrawal symptoms appear[4]. Apart from dopamine, different neurotransmitters and neuromodulators such as glutamate, noradrenaline, GABA, adenosine, vasopressin, substance P, neuropeptide Y, and nitric oxide play role in opioid withdrawal[5-7].

Topiramate is an antiepileptic agent, produced during antidiabetic drug development[8]. Unlike other antiepileptic drugs, it has monosaccharide structure containing sulfamate and approximately 40% of its weight consists of oxygen [8,9]. It has been used in the treatment of epilepsy in children and adults since 1996 and in migraine prophylaxis in adults since 2004[9,10]. Topiramate can also be used as an adjunct in the treatment of weight loss and mood disorders [11,12].

The mechanism of action of topiramate is not fully known. Firstly, it suppresses glutamatergic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptors, activates alpha-1 subregion of GABA-A receptors in the brain [13,14]. That is to say, it inhibits glutamatergic pathway-mediated neuronal excitability by stimulating the GABAergic pathway and so prevents epilepsy and migraine attacks. In addition, it is thought to contribute to the suppression of epileptogenic activity by blocking alpha subunit of voltage-gated sodium channels and voltage-gated L and R-type calcium channels[15-17]. In addition to these effects, topiramate antagonizes carbonic anhydrase enzymes (type 1, 2, 3, and 4 isoforms), which are known to play a role in diuresis, renal bicarbonate reabsorption, cerebrospinal fluid and ocular fluid production [18-20].

The effects of topiramate on addiction have been studied in experimental animals and humans. Topiramate treatment suppresses both alcohol consumption and alcohol withdrawal sings in experimental animals[21-23]. The effects of topiramate in human alcohol addiction studies have been found to be contradictory. In one of these studies, it was observed that it did not affect alcohol consumption[24], and in another, it suppressed heavy alcohol consumption[25]. The effect of topiramate on smoking in alcohol and nicotine addiction in humans has been examined, and has been shown to reduce the number of cigarettes[26]. Topiramate treatment has also been found effective in methamphetamine addiction in humans[27]. There are clinical studies showing that topiramate is effective[28] and ineffective[29] in cocaine addiction. In the study investigating alcohol dependence development mechanisms in cocaine addicted animals, it was observed that topiramate applied before alcohol intake reduced ethanol intake, but topiramate administered before cocaine intake did not cause any change in ethanol intake[30]. In a clinical study with alcohol and cocaine addicts in 2013, it

was claimed that topiramate did not suppress cocaine and alcohol consumption, but could be particularly effective in avoiding addictive substances for three weeks and adapting to treatment, especially in those with severe cocaine withdrawal [31]. The effects of topiramate have been also found contradictory in studies combined with drugs used in cocaine withdrawal in humans. In one of these studies, the combination of topiramate with methadone was ineffective[32], while in another study, its combination with amphetamine resulted positively[33].

In the morphine withdrawal study previously conducted in rats, topiramate was given intraperitoneally (i.p.) and suppressed the total behavioral score (exploring, jumping, wet dog shaking, teeth chattering, mastication) at a dose of 40 mg/kg but not at 20 mg/kg[34]. In another study with mice, topiramate suppressed only jumping of withdrawal symptoms at high dose (100 mg/kg) administered i.p. 45 min. before triggering morphine withdrawal[35].

In this study, we aimed to investigate the effects of topiramate locally applied to the nucleus accumbens, which is an important region in morphine dependence and withdrawal, on withdrawal signs and locomotor activity in naloxone-induced withdrawal syndrome.

MATERIALS AND METHODS

Animals

Twenty adult male Sprague-Dawley rats (250-300g), obtained from Marmara University Experimental Animal Center were used in the study. The research protocol was approved by the Marmara University Animal Experiments Local Ethics Committee (Approval No: 25.2017.mar). The rats were housed with a reversed 12 h light/dark cycle at 21±3°C and 50±5% humidity and had unlimited access to standard rat chow and water.

Experimental procedure

All animals underwent stereotaxic surgery under 100 mg/kg ketamine and 10 mg/kg xylazine (i.p.) anesthesia. The guide cannulas (C313; Plastics-One, Roanoke, VA) were implanted bilaterally into the NAc region (AP: +1.7 mm, ML: ± 2.0 mm and DV: -7.1 mm from bregma, with a 10-degree angle)[36]. After one week of recovery period following stereotaxic surgery, morphine dependence was rendered in all animals by subcutaneous morphine pellet implantation. Under mild ether anesthesia, a total of three morphine pellets, one on day 1 (75 mg) and two on day 3 (150 mg), were implanted subcutaneously into the intercapsular region of the rats. The animals were considered dependent on day 5[7,37] and divided into topiramate treatment (n=10) and control groups (n=10). Animals received 10 µM topiramate or saline microinjections in the topiramate and control groups, respectively, 5 min before triggering the morphine withdrawal syndrome with naloxone (3 mg/kg, i.p.). Following naloxone injection, each rat was immediately placed into a locomotor cage (AMS 9701, Commat Ltd., Istanbul, Turkey). Locomotor activity including stereotypical, ambulatory, and vertical activity and total distance covered were recorded for 15 min. Morphine withdrawal signs such as jumping and wet dog shakes were simultaneously evaluated. Weight loss, from morphine withdrawal sings was calculated by weighing just before naloxone application and just after 15 minutes of simultaneous LMA and withdrawal assessment. At the end of the experiment, high dose ketamine solution was applied to all

animals, their brains were removed for histological confirmation following cervical dislocation. Data of animals with correct placement of guide cannulas in NAc region were used for statistical evaluation.

Drugs and Solutions

Morphine pellets contained 75 mg of morphine base. Topiramate (Sigma-T0575) was dissolved in 0.9% saline solution. Rats received bilaterally 10 µM of topiramate in 250 nL volume and saline microinjections prior to 3 mg/kg i.p. naloxone hydrochloride dihydrate (Sigma-N7758) injection on day 5 of the experiment.

Statistical Analysis

All data were expressed as mean±standard error of mean (SEM). The GraphPad Prism 5.01 software was used for the analysis of the data. Two-tailed unpaired t-test was used for the analysis of withdrawal signs and locomotor activity. For all statistical calculations, significance was considered as $p<0.05$.

RESULTS

The effects of local administration of topiramate into the NAc region on naloxone-induced morphine withdrawal signs

The number of jumpings was significantly suppressed ($t=2.52$, $df=12$, $p<0.05$; Fig. 1A) in the topiramate group (1.2±1.0) compared with the control group (7.2±2.7). There was no statistically significant difference in the wet dog shake behavior ($t=0.3$, $df=12$, $p=0.76$; Fig. 1B) in topiramate group (11.2±2.8) compared with the control group (10±1.5). Weight loss was significantly suppressed ($t=3.2$, $df=12$, $p<0.01$; Fig. 1C) in the topiramate group (12.1±1.7) compared with the control group (19.8±0.8).

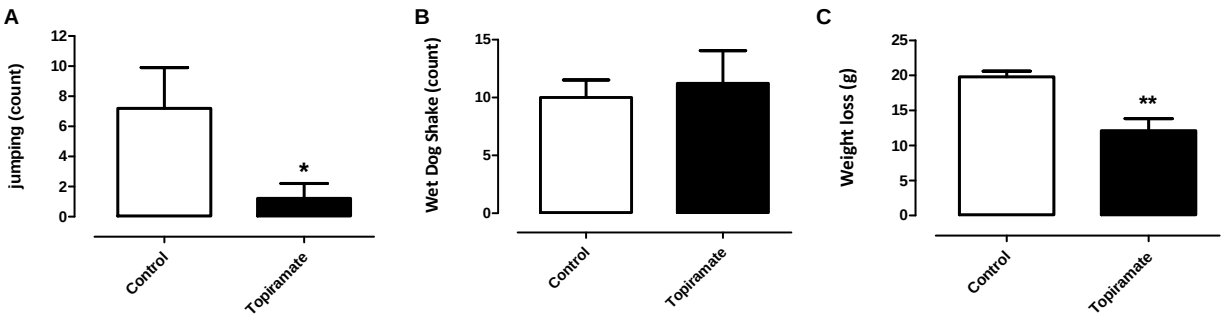

Figure 1. The effects of local administration of saline (control group, n=10) or 10 µM topiramate (topiramate group, n=10) into the NAc on A) jumping behavior, B) wet-dog shake, and C) weight loss of animals during morphine withdrawal induced by naloxone (3 mg/kg, i.p.). Results were expressed as mean±SEM, *p<0.05, **p<0.01.

The effects of local administration of topiramate into the NAc region on locomotor activity during naloxone-induced morphine withdrawal

Stereotypic activity ($t=2.36$, $df=12$, $p<0.05$; Fig. 2A) was significantly increased in topiramte group (801±74) when compared with the control group (537±66). However, there was no significant difference between topiramate and control groups in other parameters of locomotor activity, such as ambulatory activity (Fig. 2B), vertical activity (Fig. 2C) and total distance covered (Fig. 2D).

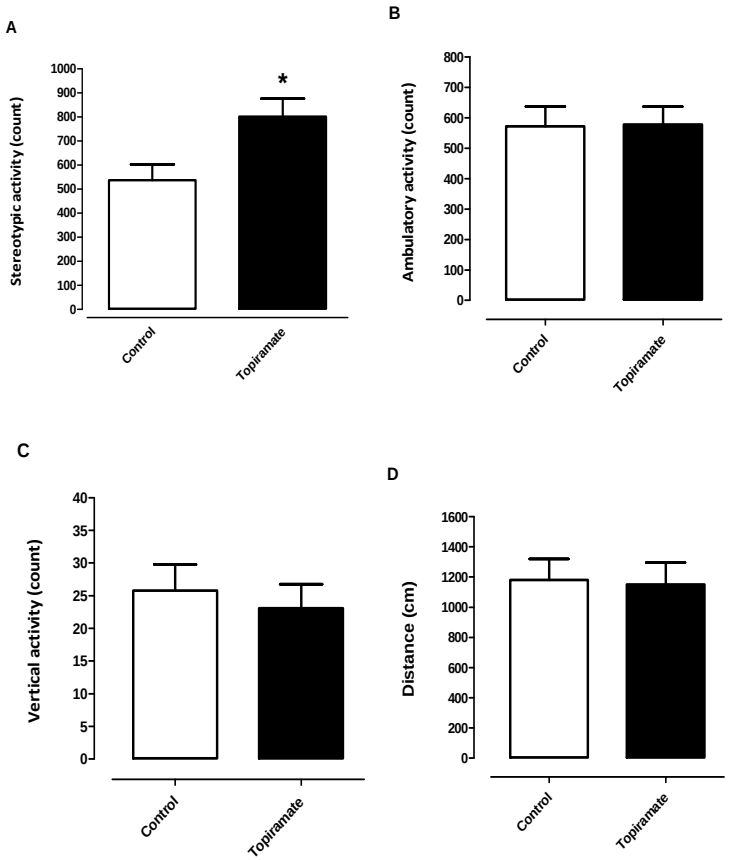

Figure 2. The effects of saline or 10 µM topiramate administration into the NAc on the locomotor activity in morphine dependent rats induced by naloxone (3 mg/kg, i.p.); A) stereotypic activity, B) ambulatory activity, C9 vertical activity and D) distance. Ten animals were used in each group, results were expressed with mean±SEM, *p<0.05.

DISCUSSION

The primary finding of our study is that, the local administration of topiramate to the NAc, which is known for its importance in addiction mechanisms, significantly reduces the number of jumpings during naloxone-induced withdrawal syndrome in morphine-dependent rats. The jumping behavior seen in mice and rats during morphine withdrawal associates with dopamine receptors, and are considered as one of the most important findings of drug-craving and -seeking[38]. Systemically administration of topiramate has been previously tested in alcohol withdrawal in experimental animals and has been shown to suppress withdrawal symptoms[23]. Topiramate treatment also exhibits anxiolytic effect in both early and late periods of alcohol withdrawal[39]. Few studies have examined the effects of topiramate on morphine withdrawal. In a recent study, systemically administered topiramate suppressed the total behavioral score, including jumping behavior in dose-dependent manner during naloxone-induced withdrawal in rats, and this finding was associated with the suppression of glutamatergic transmission in the locus coeruleus region responsible for hyperactivity during abstinence[34]. Similar suppression in withdrawal findings was observed with riluzole, one of the drugs that inhibit glutamate release[40].

Systemic administration of topiramate has been shown to reduce the jumping behavior during morphine withdrawal in mice in a dose-dependent way, and this finding was also been associated with direct suppression of the glutamatergic AMPA receptors[35]. In a case report consisting of three patients, topiramate was found effective in the treatment of opioid withdrawal[41]. The suppression in the jumping behavior in our study is compatible with these studies, but the difference of our study is that,

this result is obtained by applying topiramate directly to the NAc region for the first time. The ameliorating effect of topiramate on jumping behavior from withdrawal symptoms may be due to the suppression in glutamatergic transmission as well as dopaminergic activity as supported by the above-mentioned literature. At this point, it is necessary to question the effects of the subtypes of glutamatergic receptors. Previous studies have shown the role of glutamatergic NMDA receptors in opioid dependence and withdrawal[42,43].

In cocaine self-administration and withdrawal, the expression of glutamatergic AMPA receptors in the NAc are increased, and the blockade of AMPA receptors reduces the drug-craving [44,45]. In another study, AMPA receptor antagonists have been shown to suppress the development of tolerance in morphine dependence in mice and jumping behavior in naloxone-induced morphine abstinence[46]. These results suggest that the jumping behavior, which is the finding we obtained in our study, may have occurred through AMPA receptors. Topiramate is known to act on GABA receptors, as well as glutamatergic receptors[13,14]. In this case, the suppression in jumping behavior may have occurred through GABA receptors as well as glutamatergic receptors. As a matter of fact, we have shown in a previous study that, GABA agonists effectively reduce withdrawal symptoms in this region[6]. Considering that topiramate reduces nitric oxide-cGMP production[47], it may have contributed to the suppression of jumping behavior by inhibition of NOS, as in our previous study[5].

Wet dog shake is another symptom of naloxone-induced morphine abstinence in mice and rats. In previous studies, wet dog shaking behavior was thought to be related to serotonin[48]. In our study, the wet dog shake behavior in naloxone-induced morphine withdrawal syndrome did not cause a statistically significant change after local administration of topiramate to the NAc region. This finding shows that, serotonergic receptors do not mediate the effect of topiramate in the NAc region in morphine withdrawal.

The third finding we obtained in our study is that, the local application of topiramate to the NAc reduces weight loss during morphine withdrawal. The use of morphine suppresses gastrointestinal motility, slows gastrointestinal passage, increases anal sphincter tone and delays the emptying of intestinal contents, which facilitates a ground for constipation, as well as deepens the constipation by reducing the secretion of the gastric, pancreatic, intestinal, bile, and increasing the water absorption from chyme[49]. Administration of naloxone and similar opioid antagonists reverses the constipation and even causes diarrhea and leads to weight loss[50,51]. In a study examining the diarrhea and weight loss in the morphine withdrawal as a central or peripheral effect, morphine was administered to the brain (i.c.v.) and systematically (s.c.), diarrhea was found similar via both routes during naloxone-induced withdrawal, while weight loss was higher after s.c. administration, but also occurred after i.c.v. administration[52]. This finding shows that, the weight loss in withdrawal syndrome can occur as a result of the central effect as well as peripheral effect. Indeed, we observed the reduction in weight loss by administration topiramate to the brain, NAc region in naloxone-induced withdrawal syndrome.

Another finding we obtained in this study was that, the local administration of topiramate to the NAc increased stereotypic movements, without significant changes in other locomotor activity parameters in morphine withdrawal. It is known that the structure responsible for stereotypical behaviors are the

basal ganglia, that includes substantia nigra, subthalamic nucleus and NAc[53,54]. In opioid withdrawal, stereotypical movements which is among locomotor activity behaviors, increase[55]. It has been considered that this increase may be related to the neuroadaptation mechanisms such as dopaminergic system, change in c-fos levels, which are developed due to the repeated opioid exposure[56,57]. This finding in our study may suggest that, the effect of topiramate on opioid withdrawal is not only limited to the dopaminergic system, which involves NAc as well, that it may directly influence the substantia nigra and subthalamic nucleus related nigrostriatal pathway, or indirectly by stimulating the GABA receptors and/or by suppressing glutamatergic receptors.

CONCLUSION

Microinjection of the anticonvulsant drug topiramate to the NAc region resulted in a significant reduction in withdrawal signs during naloxone-induced withdrawal syndrome in morphine-dependent animals. Topiramate affects central and peripheral withdrawal symptoms by suppressing jumping behavior and weight loss, respectively. In addition to suppressing withdrawal findings, topiramate treatment does not make any significant change on locomotor activities, and offers withdrawal treatment options without creating an opioid-like effect such as methadone. This study shows the effect of centrally administered topiramate both in the periphery and in the center, possibly in the basal ganglia as well as NAc. However, we aim to carry out further studies to explain the mechanism of action of topiramate.

Disclosure Statement

The authors have no conflicts of interest to declare.

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The research protocol was approved by the Marmara University Animal Experiments Local Ethics Committee (Approval No: 25.2017.mar).