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The effect of acute topiramate administration on morphine withdrawal syndrome and brain-derived neurotrophic factor in central nervous system

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ABSTRACT

Objectives: Nucleus accumbens plays an important role in opioid addiction. Topiramate, increases postsynaptic gamma-aminobutyric acid receptor activity and antagonizes glutamatergic activity. Brain-derived neurotrophic factor (BDNF), which plays a key role in synaptic plasticity, is produced from proBDNF. The aim of this study is to investigate the effects of 100 µM topiramate applied into the lateral ventricle or nucleus accumbens on naloxone-induced morphine withdrawal and the BDNF/proBDNF ratio in the frontal cortex.

Methods: In the study, 36 adult male Wistar rats weighing 250–350 g were used. Morphine dependence was created with morphine pellets following guide cannula implantations. Withdrawal findings were evaluated in naloxone-induced morphine withdrawal syndrome following topiramate administration, and locomotor activity measurements were performed simultaneously. The brains of sacrificed animals were removed for determination of BDNF/proBDNF ratio.

Results: Topiramate administered by either route significantly suppressed the number of jumps in morphine withdrawal. Topiramate applied into the nucleus accumbens significantly reduced stereotypical behavior in morphine withdrawal, but did not cause any changes in other locomotor activity behaviors. Topiramate applied into the lateral ventricle significantly decreased the BDNF/proBDNF ratio, whereas administered into the nucleus accumbens significantly increased this ratio.

Conclusion: The findings of this study indicate that topiramate administered into the lateral ventricle and nucleus accumbens reduces naloxone-induced morphine withdrawal symptoms, stereotypical locomotor activity, and changes the BDNF/proBDNF ratio.

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KEYWORDS
Anticonvulsant; mBDNF; nucleus accumbens; opioid; proBDNF

Introduction

The targets of chronically used morphine and other addictive substances include the mesocorticolimbic dopaminergic system, which has a critical role in the reward mechanism [1] [2]. The dopaminergic neurons originating from the ventral tegmental area (VTA) are activated depending on the addictive substance use, and this activation causes to an increase in the dopamine levels in the brain regions, such as the amygdala, nucleus accumbens (NAc), hippocampus, and prefrontal cortex [3,4].

Topiramate, a new generation antiepileptic, has more than one cellular target unlike other anticonvulsants [5]. Decrease in the voltage-gated sodium currents, increase in the hyperpolarizing potassium currents, inhibition of glutamatergic α-amino -3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-kainate receptors, and increase in the postsynaptic γ-aminobutyric acid type A ($GABA_A$) receptor-mediated chloride currents are the yet known pharmacological effects of topiramate [5,6]. It has been shown in both in vitro and in vivo studies with topiramate that it exhibits neuroprotective effect and suppresses neuronal cell loss by reducing the damage, oxidative stress and inflammation caused by glutamatergic excitotoxicity [7]. The effects of topiramate on dependence have been investigated before. In studies on alcohol dependence, topiramate use decreased the alcohol consumption per day, the rate of days of heavy alcohol use and the days of alcohol use [8]. It was observed that topiramate administered before naloxone-induced withdrawal in morphine-dependent rats dose-dependently decreased the total behavioral score, and its effect on the glutamatergic mechanisms was held responsible for these effects [9]. Topiramate treatment was reported to suppress withdrawal symptoms in three patients who underwent an opiate detoxification program [10]. Topiramate, used in the treatment of 170 patients with comorbid cocaine and alcohol dependence, did not reduce cocaine and alcohol use and did not suppress cocaine craving, but good results were shown in adherence to treatment and

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abstinence from cocaine, especially in patients with severe withdrawal symptoms [11].

Brain-derived neurotrophic factor (BDNF) or mature BDNF (mBDNF) is a member of the neurotrophin family playing a role in the development, function, and survival of the neurons [12]. It is produced from proBDNF, which plays a role in apoptosis mechanisms [13]. BDNF, which is common in the central nervous system (CNS) and known to be important in synaptic plasticity, has been associated with addiction and withdrawal mechanisms as well as learning and memory [14,15]. It has been shown in a previous study that there is a positive correlation between high serum BDNF levels and craving in opiate addicted individuals [14]. It was found that BDNF levels were high in the VTA, NAc and amygdala of rats with cocaine withdrawal, and both BDNF and proBDNF levels were high in the frontal cortex of rats with morphine addiction and withdrawal [13,15].

This study aimed to investigate the effects of topiramate applied locally to the NAc region, which is known to be important in morphine dependence and withdrawal, and intracerebroventricularly (ICV) on the withdrawal symptoms and locomotor activity behavior in naloxone-induced morphine withdrawal syndrome, as well as on the BDNF/proBDNF ratio in the frontal cortex, which is known to be important in morphine seeking behavior.

Materials and methods

Animals

In this study, a total of 36 adult male Wistar rats (250–350 g) were used in 7 groups as control (saline, $n = 4$), dependent (morphine, $n = 4$), withdrawal (morphine +naloxone, $n = 4$), ICV-T (morphine+naloxone+ICV topiramate, $n = 6$), ICV-C (morphine+naloxone+ICV saline, $n = 6$), NAc-T (morphine+naloxone+topiramate into-NAc, $n = 6$), and NAc-C (morphine+naloxone+saline into-NAc, $n = 6$). Behavioral experiments used in the evaluation of withdrawal syndrome are affected by the menstrual cycle of female rats, and since these behaviors occur earlier and more severely in male rats, we preferred only male rats in our study. The study was approved by the local ethics committee MUHDEK (83.2017.mar). The rats obtained from DEHAMER were housed with a reversed 12 h light/dark cycle at 21 ± 3°C and 50 ± 5% humidity. There was unlimited access to standard rat chow and water.

Experimental procedure

Following a one-week acclimatization period, guide cannulas (C313; Plastics-One, Roanoke, VA, U.S.A) were implanted unilaterally to the lateral ventricle (AP −1.0 mm, ML −1.5 mm, and DV −3.5 mm, from bregma) of the animals in the ICV-T and ICV-C groups, bilaterally into-NAc (AP +1.7 mm, ML ±2.0 mm and DV −7.1 mm from bregma, with a 10-degree angle) of the animals in the NAc-T and NAc-C groups with standard stereotaxic surgery under ketamine ketamine-xylazine anesthesia [16]. The animals were allowed to recover from surgery for a week.

One (75 mg) and two (150 mg) slow-release morphine pellets were placed subcutaneously under mild ether anesthesia on the 1st (following the acclimatization period in the dependent and withdrawal groups, and a one-week recovery period in the animals undergoing to surgery) and 3rd days of the experiment, respectively, in all animals except the control group. Placebo pellets were implanted in the control group. Before the 1st pellet implantation, the animals in the ICV-T, ICV-C, NAc-T, and NAc-C groups were placed into a locomotor cage for 15 min for 1st locomotor activity (LMA) measurements such as stereotypic, vertical and ambulatory movements and total distance covered (AMS 9701, Commat Ltd.,). On the 5th day of the experiment, morphine withdrawal was induced by naloxone (3 mg/kg, i.p.) after saline or topiramate administration in the ICV-T, ICV-C, NAc-T, and NAc-C groups and without any additional administration in the withdrawal group and each rat was immediately placed into a locomotor cage for 2nd LMA measurement and simultaneous evaluation of morphine withdrawal symptoms, such as jumping and wet dog shakes [17,18]. Jumping and wet dog shakes were observed by the same investigator blindly and were counted. To determine body weight loss, each rat was weighed just before withdrawal was triggered and immediately after assessment of simultaneous LMA measurements and withdrawal signs. Following LMA measurement and evaluation of withdrawal signs, rats were decapitated with a guillotine, brains were collected for dissection of the frontal cortex and stored at −80°C until Western Blot analysis [19].

Western blot analysis

Western blot analysis was performed on frontal cortex samples that were homogenized in a RIPA (radioimmunoprecipitation assay buffer, Ripa-100, ECO-TECH) buffer containing protease inhibitors. The amount of protein in each homogenate was determined using the Lowry method. Protein samples stored at −80°C were mixed with 4× sample loading buffer, and then denatured for 3 min at 100°C. 30 µg of protein was loaded onto a 10% SDS-PAGE gel and electrophoresed for 100 min at 150 volts. The transfer to nitrocellulose membranes was carried out for 1.5 h, not exceeding 150 milliamps. The nitrocellulose membranes were blocked with Tris buffer saline (TBS) containing 1% bovine

serum albumin and 0.05% Tween-20, and then incubated overnight at 4°C with antibodies against BDNF and proBDNF. Separate blots were used for the specific antibodies. β-actin was used as an internal control and probed with antibodies from Santa Cruz (sc20981, US), Abcam (ac108319, UK), and Novus (nb600–532, UK). After washing the blots three times with Tween-20 (TBS-T), alkaline phosphatase-conjugated secondary antibodies from Sigma (a3812, US) were added and incubated for 1 h at 20°C. Detection of the antibody-antigen complex was performed with Nitro Blue Tetrazolium and 5-Bromo-4-Chloro-3-Indolyl Phosphate (NBT-BCIP) from Thermo Fisher (34042, Massachusetts, U.S.A). BDNF and proBDNF were quantified relative to β-actin on the blot, and the total amount of protein in each lane was normalized to the endogenous β-actin control. Densitometric analysis was performed using the free edition of the Image J Software program.

Drugs and solutions

All animals underwent stereotaxic surgery under anesthesia of 100 mg/kg ketamine (Alfamine, Alfasan, Kuipersweg, Woerden, The Netherlands) and 10 mg/kg xylazine (Basilazine, Bavet, Tuzla, Istanbul, Turkey) [20,21]. Morphine dependence was induced by subcutaneous implantation of morphine pellets containing 75 mg of morphine base. 100 µM topiramate (456190010, Acros Organics, Thermo Fisher Scientific, Geel, Belgium) ICV or into-NAc was administered before inducing morphine withdrawal with intraperitoneal (i.p.) naloxone hydrochloride dihydrate (N7758, Sigma-Aldrich, St. Louis, MO, U.S.A). Topiramate and naloxone were dissolved in saline. ICV injections were given unilaterally and in a volume of 2 µL to ICV-T and ICV-C groups. Microinjections into-NAc were given bilaterally and in a volume of 500 nL to NAc-T and NAc-C groups.

Statistical analysis

The GraphPad Prism 8 software was used for the analysis of the data. The results of the study groups were presented as mean ± standard error of mean (SEM). Parametric data two-tailed unpaired t-test was used for withdrawal symptoms and LMA analysis, and Mann-Whitney U-test was used for data analysis (data not shown) such as non-parametric ptosis and diarrhea score. A one-way analysis of variance (ANOVA) post-hoc Tukey test was used for BDNF/proBDNF analysis of control, withdrawal, and dependent groups. A two-tailed unpaired t-test was used for the analysis of ICV-C vs ICV-T group and NAc-C vs NAc-T group. For all statistical calculations, the significance was considered as $p < 0.05$.

Results

Topiramate decreased the number of jumping in naloxone-induced withdrawal. This effect was statistically significant ($p = 0.026$, $t = 2.6$, df = 10 and $p = 0.03$, $t = 2.5$, df = 10, respectively) in the ICV-T group (0.5 ± 0.3) compared to the ICV-C group (4.3 ± 1.4) and in the NAc-T group (0.5 ± 0.2) compared to the NAc-C group (2.8 ± 0.9) (Figure 1a). There was no significant difference in terms of wet dog shakes (Figure 1b) and weight loss (Figure 1c) during naloxone-induced withdrawal in the topiramate-treated ICV-T (11.2 ± 2 and 12.0 ± 1.7, respectively) and NAc-T (8.1 ± 1 and 12.0 ± 2.5, respectively) groups compared to the ICV-C (8.7 ± 1.5 and 17.7 ± 2.3, respectively) and NAc-C (12.8 ± 0.9 and 15.5 ± 2.2, respectively) groups.

The percentage change of LMA behaviors in naloxone-induced morphine withdrawal compared with the pre-withdrawal period was used in the assessment.

Topiramate did not alter stereotypic movements after ICV administration (ICV-C (107 ± 8), ICV-T (90 ± 12)) but suppressed its following administration to the NAc. This effect was statistically significant ($p = 0.009$; $t = 3.07$; df = 12, Figure 2a) in the NAc-T group

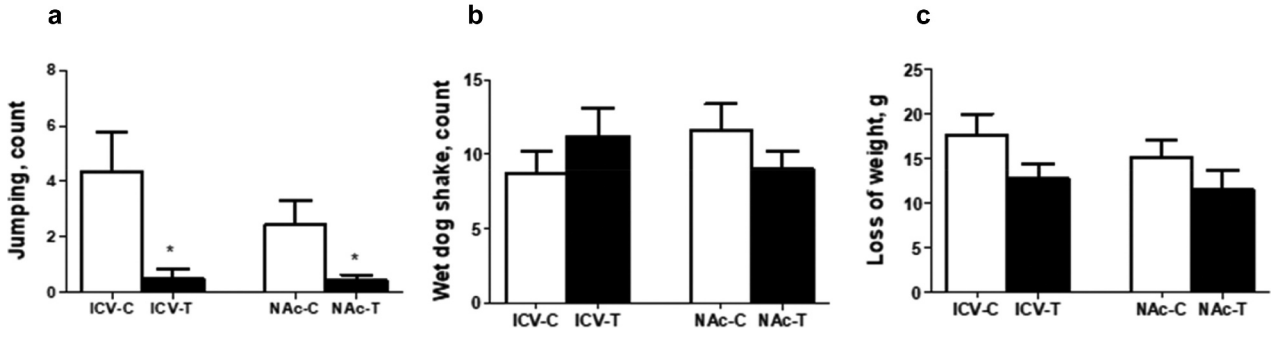

Figure 1. The effects of 100 µM topiramate applied ICV (ICV-T, $n = 6$) and to the NAc (NAc-T, $n = 6$) on jumping (A), wet dog shakes (B) and loss of weight (C) in naloxone-induced morphine withdrawal. Saline was administered ICV (ICV-C, $n = 6$) and into-NAc (NAc-C, $n = 6$) to the control groups in the same volume. Two-tailed unpaired t-test was used for the analysis of withdrawal signs, results were expressed with mean±SEM, *p < 0.05.

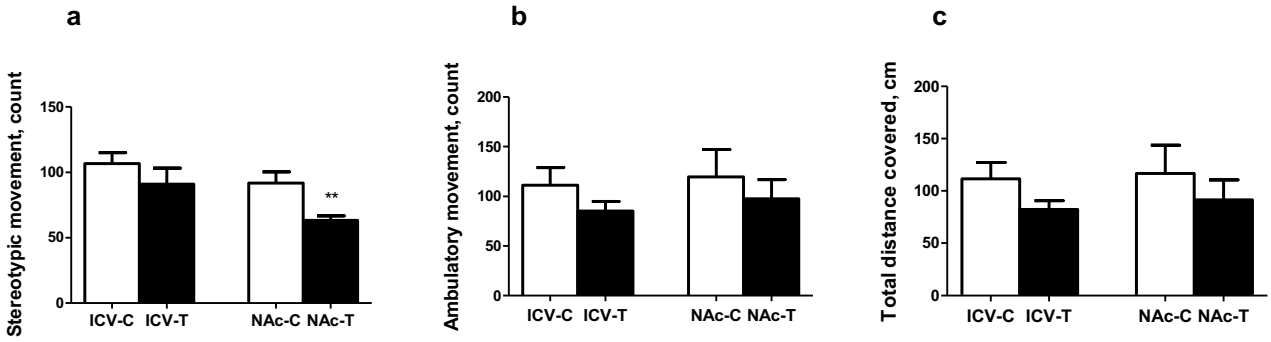

Figure 2. The effects of 100 µM topiramate applied ICV (ICV-T, $n = 6$) and to the NAc (NAc-T, $n = 6$) on stereotypic movements (A), ambulatory movements (B) and total distance covered (C) in naloxone-induced morphine withdrawal. Saline was administered ICV (ICV-C, $n = 6$) and to the NAc (NAc-C, $n = 6$) to the control groups in the same volume. Two-tailed unpaired t-test was used for the analysis of withdrawal signs, results were expressed with mean±SEM, **p < 0.01.

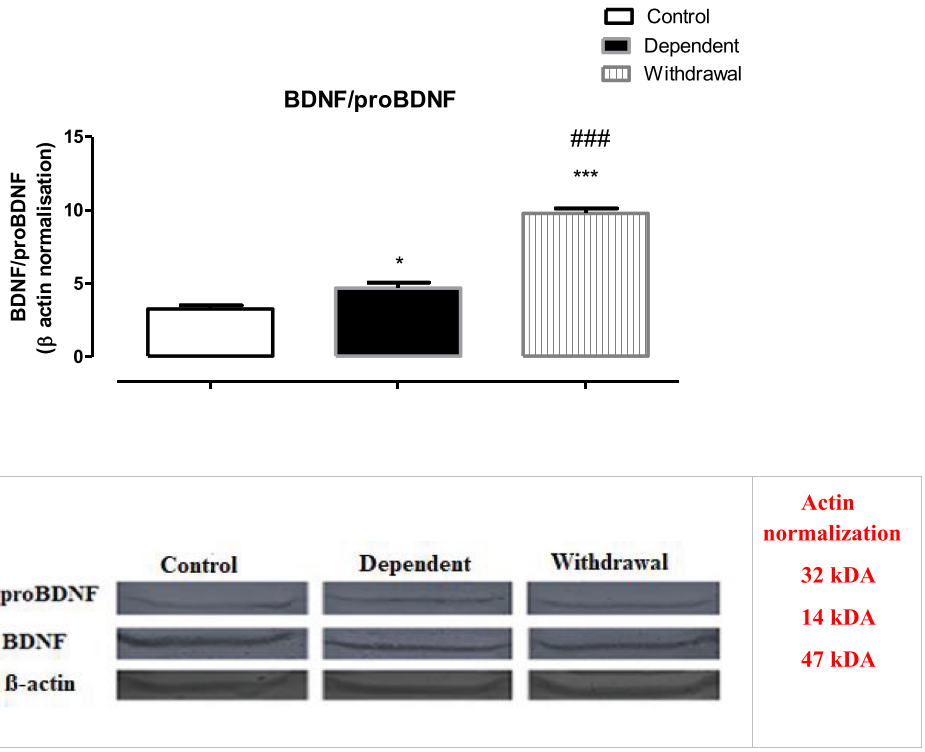

Figure 3. The effects of morphine addiction (dependent group, $n = 4$) and withdrawal (withdrawal group, $n = 4$) on BDNF/proBDNF ratio measured in frontal cortex homogenate. Placebo pellets were implanted in the control group ($n = 4$). Each band represents the amount of protein of BDNF, proBDNF and ß-actin antibodies in homogenates containing 30 µg protein. One-way analysis of variance (ANOVA) post-hoc Tukey's test was used, results were expressed with mean±SEM, *p < 0.05 and ***p < 0.001 compared to control group, ###p < 0.001 compared to dependent group.

(64 ± 4) compared to the NAc-C group (95 ± 9). No significant differences were observed in the ambulatory movements (Figure 2b) and total distance covered (Figure 2c) in naloxone-induced withdrawal between the ICV-T (85 ± 10 and 82 ± 8, respectively), ICV-C (111 ± 18 and 111 ± 15, respectively), NAc-T (106 ± 20 and 100 ± 20, respectively) and NAc-C (126 ± 32 and 122 ± 31, respectively) groups.

BDNF/proBDNF ratio increased in the dependent (4.7 ± 0.4) and withdrawal (9.8 ± 0.3) groups compared to the control group (3.3 ± 0.2). This increase was statistically significant ($p < 0.0001$, F = 118.9, Figure 3).

Topiramate decreased the BDNF/proBDNF ratio following the ICV administration, but increased it after administration into-NAc. These effects were statistically significant ($p = 0.0038$; $t = 4.57$, df = 6 and $p = 0.0014$, $t = 5.58$, df = 6, respectively) in the ICV-T group (2.76 ± 0.21) compared to the ICV-C group (4.26 ± 0.25) and in the NAc-T group (6.04 ± 0.29) compared to the NAc-C group (3.59 ± 0.33) (Figure 4).

Discussion

In this study, we investigated the effects of topiramate on NAc and ICV administration on morphine

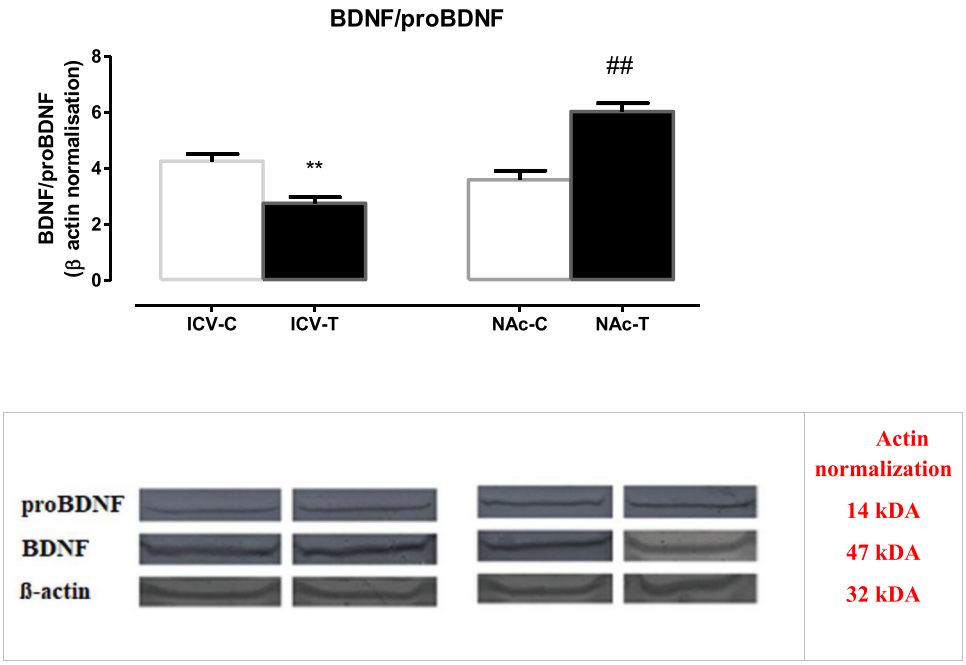

Figure 4. The effects of 100 µM topiramate applied ICV (ICV-T, $n = 6$) and into-NAc (NAc-T, $n = 6$) on BDNF/proBDNF ratio measured in frontal cortex homogenate during naloxone-induced morphine withdrawal. Saline was administered ICV (ICV-C, $n = 6$) and into-NAc (NAc-C, $n = 6$) to the control groups in the same volüme. Each band represents the amount of protein of BDNF, proBDNF and ß-actin antibodies in homogenates containing 30 µg protein. Two-tailed unpaired t-test was used for the analysis of withdrawal signs, results were e.

withdrawal and neurotrophic factors. NAc is one of the regions in the mesocorticolimbic dopaminergic system, which has a critical role in the reward mechanism resulting from chronic use of addictive substances, and where dopamine levels increase as a result of the activation of VTA-derived dopaminergic neurons. While we aimed to see the effect of topiramate in all regions of the mesocorticolimbic dopaminergic system with ICV administration, we wanted to see the effects specific to this region and at the dose we preferred in intra-NAc administration. Another reason for administering topiramate locally into this region is that we want to see its NAc-mediated effects on withdrawal symptoms without affecting glutamatergic and GABAergic projections from the cortex and VTA.

The primary finding in our study is that topiramate administered ICV and to the NAc significantly suppressed the jumping behavior in naloxone-induced morphine withdrawal syndrome. Jumping is the withdrawal behavior of rats, it's an important indicator of the degree of addiction, and has been associated with the dopaminergic system [18,22]. In animal studies in which opioid dependence was not developed and withdrawal was not triggered, it has been shown that the dopamine precursor L-DOPA alone or in combination with the CNS stimulant amphetamine caused opioid withdrawal like jumping, and this effect was prevented with dopamine antagonists [22]. In another study, it was observed that L-DOPA and apomorphine administered before naloxone-induced abstinence in morphine-dependent mice potentiated jumping behavior in a dose-dependent manner, while the dopamine antagonists, on the contrary, suppressed the jumping behavior [18]. VTA-derived dopaminergic neurons extend to the NAc, which has a key role in the reward system, dopamine levels increase in the NAc during addiction and decrease during withdrawal [4]. The jumping behavior associated with the dopaminergic system in withdrawal syndrome was also associated with glutamatergic receptors [23–26]. The upregulation of AMPA in the NAc is known to be important in the development of addiction and withdrawal syndrome [23]. In a previous study with mice, both AMPA and NMDA receptor antagonists were shown to reduce the naloxone-induced jumping behavior [24,25]. In another study with rats, chronic ICV administration of selective and non-selective antagonists of $mGluR_{2,3}$, one of the metabotropic glutamate receptor (mGluR) subtypes, suppressed the naloxone-induced jumping behavior [26]. The role of GABA neurotransmission in naloxone-induced morphine withdrawal should not be ignored [2,27]. In the study conducted with baclofen, a GABA agonist applied to the NAc, it was observed that it reduced the number of jumps in naloxone-induced withdrawal syndrome [2]. Considering the effects of topiramate on AMPA-kainate receptors, it's both ICV and intra-NAc application reduced the naloxone-induced jumping behavior compared to the control groups, may be due to its inhibition of AMPA receptors with direct effect and/or modulation of dopaminergic transmission via AMPA receptors with indirect effect [5]. In

addition, the fact that topiramate changes GABA neurotransmission, known to play a role in morphine withdrawal, by increasing postsynaptic $GABA_A$ receptor-mediated currents, may also have a suppressive effect on naloxone-induced jumping behavior [6].

The ICV and intra-NAc administration of topiramate did not cause a significant change in the wet dog shake, compared to the control group. According to the studies, the wet dog shake is mediated by the serotonergic system [28]. Intraventricular administration of serotonin causes wet dog shake in rats, but morphine and mianserin, a serotonin receptor antagonist, reverse this effect [28]. In the same study, the effects of naloxone application on the wet dog shake triggered by serotonin, which was eliminated by morphine and mianserin, were also examined, and it was observed that the wet dog shakes were repeated in morphine-treated animals, but not after mianserin application [28]. In a study with mice, it was shown that chronic morphine treatment caused an increase in the expression of serotonergic 5-HT2C receptors in the VTA, NAc, and locus coeruleus, and stimulation of this receptor with lorcaserin, an agonist of this receptor, reduced wet dog shakes [29]. In addition to serotonergic pathways, GABAergic pathways also play a role in wet dog shake [2,30]. The GABA agonist baclofen suppressed naloxone-induced wet dog shake, whereas the competitive antagonist of $GABA_A$ bicuculline did not alter this behavior, but 5-hydroxytryptophan reversed it [2,30]. In our study, topiramate administered both ICV and intra-NAc did not cause a significant change in wet dog shake, one of the naloxone-induced morphine withdrawal signs suggests that it does not affect the serotonergic system directly or indirectly through $GABA_A$ and AMPA-kainate receptors in morphine withdrawal syndrome.

Morphine causes constipation by suppressing gastrointestinal motility with its peripheral effect, while naloxone antagonizes this effect and causes diarrhea [31]. In our study, topiramate administered to rats in both ICV-T and NAc-T groups did not change the weight loss in naloxone-induced morphine withdrawal syndrome compared to the control group. In previous studies, it has been shown that the GABA agonist baclofen applied both systemically and locally to the NAc, reduces weight loss in naloxone-induced withdrawal syndrome [2,27]. Based on this information, topiramate would be expected to alleviate weight loss in naloxone-induced morphine withdrawal, such as GABA agonists, by increasing postsynaptic $GABA_A$ receptor-mediated currents. The fact that topiramate does not mediate the peripheral effects of withdrawal, such as weight loss, indicates that its effect is mediated by modulation of AMPA receptors, such as wet dog shake, rather via GABA receptors. One of the remarkable findings of our study is that ICV topiramate administration in naloxone-induced morphine withdrawal syndrome did not change the percentage change of stereotypic movements, which is one of the LMA behaviors, compared to the control group, local application of topiramate to the NAc significantly reduced it. In addition to withdrawal symptoms, locomotor activity, especially stereotypical behaviors, are known to increase in withdrawal syndrome [32]. Previous studies have shown that stereotypical behavior is associated with dopaminergic receptors and increases 3–5 times in morphine withdrawal [33]. The dopamine released from nigrostriatal and mesolimbic dopaminergic nerve terminals as the neurotransmitter and basal ganglia including substantia nigra, subthalamic nucleus and NAc as the region were held responsible for the increasing stereotypic movements in withdrawal syndrome [34]. In a study with rats, it was shown that the systemic administration of GABA agonist baclofen caused a significant decrease in stereotypic head movements in naloxone-induced morphine withdrawal syndrome, while inducible with baclofen, the $GABA_B$ receptor antagonist reversed this effect [27]. In our study, it can be said that topiramate administered to the NAC reduces stereotypical behaviors in withdrawal compared to the control and ICV-administered topiramate groups, through GABA receptor-mediated GABAergic activity modulation of dopaminergic system or dopamine release in the same region. The lack of suppressive effect of topiramate on stereotypic movements during ICV administration may be due to the glutamatergic modulation of GABA receptor-mediated GABAergic activity originating from the VTA and/or cortex, which innervates this region other than the NAc.

In our study, administration of topiramate to the rats in both ICV-T and NAc-T groups did not cause a significant change in the percentage change of ambulatory movements and total distance covered in naloxone-induced morphine withdrawal syndrome compared with the control group. The reason for this may be that ambulatory movements and total distance covered are not affected by topiramate-mediated increase in GABAergic activity and/or suppression of glutamatergic activity, or that the topiramate-mediated effect is reversed by dopaminergic, glutamatergic, etc. pathways. Considering that topiramate reduces the jumping, which is one of the withdrawal symptoms, and the stereotypic movements from the LMA behaviors, we can say that topiramate applied to both ICV and intra-NAC reduces the withdrawal symptoms without changing the motor coordination of the animals.

We observed that the BDNF/proBDNF ratio significantly increased in the frontal cortex in both morphine dependence and morphine withdrawal. In a study with rats, an increase in BDNF levels

and its receptor TrkB expression in the frontal cortex, and an increase in BDNF levels in the hippocampus and midbrain were observed in withdrawal syndrome triggered by cutting the morphine use [35]. In another study, it was shown that both morphine administration and morphine withdrawal significantly increased the BDNF and proBDNF levels in the frontal cortex compared to control groups, which is consistent with the findings in our study [13]. This relative increase we observed in the BDNF levels in morphine dependence and withdrawal may have developed as a neuroprotective reaction or an adaptation mechanism [36]. In naloxone-induced morphine withdrawal syndrome, ICV administration of topiramate caused a significant decrease in the BDNF/proBDNF ratio in the frontal cortex compared to the control group, while its local application to the NAc caused a significant increase. In a study in which the AMPA receptor potentiator and its active isomer were administered to the rats, a significant increase was observed in the number of BDNF-immunopositive cells in the dentate gyrus of the hippocampus [37]. BDNF can also alter the AMPA receptor subunit expression and trafficking in different in vitro systems [38]. Considering the relationship between AMPA and GABA receptors, distributed in different parts of the brain, and BDNF, widely expressed in glutamatergic neurons in the frontal cortex and dopaminergic pathways in the mesolimbic system, the increase in the BDNF/proBDNF ratio after local application to the NAc region indicates the modulatory effect of topiramate on brain protection. The decrease in the BDNF/proBDNF ratio due to ICV topiramate administration indicates that the indirect neuroprotective effect due to the conversion of proBDNF to BDNF will occur in the late period, and that the neuroprotective role of the NAc is at the forefront.

Conclusions

In this study, topiramate applied to the brain reduced jumping, one of the most important symptoms of morphine withdrawal syndrome, and stereotypical behaviors closely related to withdrawal and dopamine without changing motor coordination. Topiramate applied locally to the NAc significantly increased the ratio of neuroprotective BDNF and apoptotic proBDNF in the frontal cortex. Topiramate may achieve these effects through GABA currents, as well as over glutamate receptors. In future studies, examining the effects of topiramate at the level of GABA and glutamate receptors in addiction and the contribution of the change in the BDNF/proBDNF cycle will shed light on our understanding of addiction mechanisms.

Disclosure statement

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References

[1] Yananli H, Gören MZ, Berkman K, et al. Effect of agmatine on brain L-citrulline production during morphine withdrawal in rats: a microdialysis study in nucleus accumbens. Brain Res. 2007;1132:51–58.
[2] Topkara B, Yananli HR, Sakallı E, et al. Effects of injection of gamma-aminobutyric acid agonists into the nucleus accumbens on naloxone-induced morphine withdrawal. Pharmacology. 2017;100:131–138.
[3] Jafarova Demirkapu M, Raci Yananli H (February 27th 2020). Opium Alkaloids, Bioactive Compounds in Nutraceutical and Functional Food for Good Human Health, Kavita Sharma, Kanchan Mishra, Kula Kamal Senapati and Corina Danciu, IntechOpen. Available from: https://www.intechopen.com/chapters/71219 accessed 1 May 2022.
[4] Jafarova Demirkapu M, Yananli HR, Kaleli M, et al. The role of adenosine A1 receptors in the nucleus accumbens during morphine withdrawal. Clin Exp Pharmacol Physiol. 2020;47(4):553–560.
[5] Walker MC, Sander JW. Topiramate: a new antiepileptic drug for refractory epilepsy. Seizure. 1996;5:199–203.
[6] Herrero AI, Del Olmo N, González-Escalada JR, et al. Two new actions of topiramate: inhibition of depolarizing GABA(A)-mediated responses and activation of a potassium conductance. Neuropharmacology. 2002;42(2):210–220.
[7] Motaghinejad M, Motevalian M, Shabab B. Neuroprotective effects of various doses of topiramate against methylphenidate induced oxidative stress and inflammation in rat isolated hippocampus. Clin Exp Pharmacol Physiol. 2016;43(3):360–371.
[8] Johnson BA, Rosenthal N, Capece JA, et al. Topiramate for Treating Alcohol Dependence: a Randomized Controlled Trial. JAMA. 2007;298(14):1641–1651. DOI:10.1001/jama.298.14.1641
[9] Medrano MC, Mendiguren A, Pineda J. Effect of ceftriaxone and topiramate treatments on naltrexone-precipitated morphine withdrawal and glutamate receptor desensitization in the rat locus coeruleus. Psychopharmacol (Berl). 2015;232:2795–2809.

[10] Zullino DF, Cottier AC, Besson J. Topiramate in opiate withdrawal. Prog Neuro-Psychopharmacol Biological Psychiatry. 2002;26(6):1221–1223.
[11] Kampman KM, Pettinati HM, Lynch KG, et al. A double-blind, placebo-controlled trial of topiramate for the treatment of comorbid cocaine and alcohol dependence. Drug Alcohol Depend. 2013;133 (1):94–99.
[12] Binder DK, Scharfman HE. Brain-derived neurotrophic factor. Growth Factors. 2004;22(3):123–131.
[13] Bachis A, Campbell LA, Jenkins K, et al. Morphine Withdrawal Increases Brain-Derived Neurotrophic Factor Precursor. Neurotox Res. 2017;32:509–517.
[14] Heberlein A, Dürsteler-MacFarland KM, Lenz B, et al. Serum levels of BDNF are associated with craving in opiate-dependent patients. J Psychopharmacol. 2011;25:1480–1484.
[15] Grimm JW, Lu L, Hayashi T, et al. Time-dependent increases in brain-derived neurotrophic factor protein levels within the mesolimbic dopamine system after withdrawal from cocaine: implications for incubation of cocaine craving. J Neurosci. 2003;23:742–747.
[16] Paxinos G, Watson C. The Rat Brain in Stereotaxic Coordinates. 6th ed. San Diego: Elsevier Academic Press; 2007.
[17] Pinelli A, Trivulzio S. Quantitative evaluation of opioid withdrawal signs in rats repeatedly treated with morphine and injected with naloxone, in the absence or presence of the antiabstinence agent clonidine. J Pharmacol Toxicol Methods. 1997;38:117–131.
[18] el-Kadi AO, Sharif SI. The role of dopamine in the expression of morphine withdrawal. Gen Pharmacol. 1998;30(4):499–505.
[19] Chiu K, Lau WM, Lau HT, et al. Micro-dissection of rat brain for RNA or protein extraction from specific brain region. J Vis Exp. 2007;7:269.
[20] JW G 3rd, Sombati S, DeLorenzo RJ, et al. Cellular actions of topiramate: blockade of kainate-evoked inward currents in cultured hippocampal neurons. Epilepsia. 2000;41(S1):10–16.
[21] Mao XY, Cao YG, Ji Z, et al. Topiramate protects against glutamate excitotoxicity via activating BDNF/TrkB-dependent ERK pathway in rodent hippocampal neurons. Prog Neuropsychopharmacol Biol Psychiatry. 2015;60:11–17.
[22] Lal H, Colpaert FC, Laduron P. Narcotic withdrawal like mouse jumping produced by amphetamine and L-DOPA. Eur J Pharmacol. 1975;30:113–116.
[23] Hearing M. Prefrontal-accumbens opioid plasticity: implications for relapse and dependence. Pharmacol Res. 2019;139:158–165.
[24] McLemore GL, Kest B, Inturrisi CE. The effects of LY293558, an AMPA receptor antagonist, on acute and chronic morphine dependence. Brain Res. 1997;778:120–126.
[25] Kamali M, Sahraei H, Khosravi M, et al. Asymmetric Involvement of Central and the Peripheral NMDA Glutamate Receptors in the Expression of Withdrawal Syndrome in Morphine-Dependent Mice. Physiol Pharmacol. 2016;19:274–284.
[26] Fundytus ME, Ritchie J, Coderre TJ. Attenuation of morphine withdrawal symptoms by subtype selective metabotropic glutamate receptor antagonists. Br J Pharmacol. 1997;120:1015–1020.
[27] Bexis S, Ong J, White J. Attenuation of morphine withdrawal signs by the GABA(B) receptor agonist baclofen. Life Sci. 2001;70:395–401.
[28] Drust EG, Sloviter RS, Connor JD. Effect of morphine on 'wet-dog' shakes caused by cerebroventricular injection of serotonin. Pharmacology. 1979;18:299–305.
[29] Zhang G, Wu X, Zhang YM, et al. Activation of serotonin 5-HT(2C) receptor suppresses behavioral sensitization and naloxone-precipitated withdrawal symptoms in morphine-dependent mice. Neuropharmacology. 2016;101:246–254.
[30] Kruszewska A. The role of GABA in morphine abstinence in rats. Drug Alcohol Depend. 1988;21:37–41.
[31] Suzuki T, Hayashi Y, Misawa M. The role of mu 1 receptor in physical dependence on morphine using the mu receptor deficient CXBK mouse. Life Sci. 1992;50:849–856.
[32] Druhan JP, Walters CL, Aston-Jones G. Behavioral activation induced by D(2)-like receptor stimulation during opiate withdrawal. J Pharmacol Exp Ther. 2000;294(2):531–538.
[33] Lee JM, DeLeon-Jones F, Fields JZ, et al. Cyclo (Leu-Gly) attenuates the striatal dopaminergic supersensitivity induced by chronic morphine. Alcohol Drug Res. 1987;7(1):1–10.
[34] Pappas SS, Leventhal DK, Albin RL, et al. Mouse models of neurodevelopmental disease of the basal ganglia and associated circuits. Curr Top Dev Biol. 2014;109:97–169.
[35] Peregud DI, Yakovlev AA, Stepanichev MY, et al. Expression of BDNF and TrkB Phosphorylation in the Rat Frontal Cortex During Morphine Withdrawal are NO Dependent. Cell Mol Neurobiol. 2016;36:839–849.
[36] Bathina S, Das UN. Brain-derived neurotrophic factor and its clinical implications. Arch Med Sci. 2015;11:1164–1178.
[37] Mackowiak M, O'Neill MJ, Hicks CA, et al. An AMPA receptor potentiator modulates hippocampal expression of BDNF: an in vivo study. Neuropharmacology. 2002;43:1–10.
[38] Li X, Wolf ME. Multiple faces of BDNF in cocaine addiction. Behav Brain Res. 2015;279:240–254.