Available online at www.sciencedirect.com
ScienceDirect
Progress in Neuro-Psychopharmacology & Biological Psychiatry 31 (2007) 525–528
Progress In Neuro-Psychopharmacology & Biological Psychiatry
www.elsevier.com/locate/pnpbp

Effect of repeated treatment with topiramate on the beta-endorphin plasma level in rats selectively bred for high and low alcohol preference

Jadwiga Zalewska-Kaszubska [a,*], Dorota Gorska [a], Wanda Dyr [b], Elzbieta Czarnecka [a]

[a] Department of Pharmacodynamics, Medical University of Lodz, Muszynskiego 1, PL 90–151 Lodz, Poland
[b] Department of Pharmacology and Physiology of the Nervous System, Institute of Psychiatry and Neurology, Warsaw, Poland

Received 30 August 2006; received in revised form 6 December 2006; accepted 6 December 2006
Available online 9 January 2007

Abstract

Recent research indicates that topiramate has a role in the treatment of alcohol dependence. Topiramate has multiple mechanisms of action including enhancement of GABA-ergic inhibitory transmission and blocking excitatory glutamate neurotransmission, and modulating voltage-gated sodium and calcium ion channels and inhibiting carbonic anhydrase. In this study, we examined the effect of topiramate on endogenous opioid systems, which have an important role in the development of alcohol dependence. We investigated the beta-endorphin plasma level of animals with high- and low-risks of alcohol dependency after repeated treatment with topiramate. We used the Warsaw High Preferring (WHP) and Warsaw Low Preferring (WLP) rats, and treated them with topiramate at a dose of 80 mg/kg p.o. for 14 days. In WHP rats treatment with topiramate led to an increase in beta-endorphin plasma levels, which persisted at the same level even after a single injection of alcohol. The level of this peptide with topiramate was lower than in alcohol-injected WHP rats who did not receive topiramate. Beta-endorphin levels in WHP rats after topiramate or topiramate and ethanol treatment were similar to the basal level of this peptide in WLP rats. In WLP rats, topiramate did not prevent the ethanol-induced increase in beta-endorphin plasma level.

We propose that administration of topiramate may have different effects on the opioid system involved in dependence according to genetic susceptibilities to alcoholism.

Keywords: Alcohol preferring rats; Beta-endorphin; Ethanol; Topiramate

1. Introduction

Relapse in alcohol-dependent patients can be prevented with several agents that reduce craving for alcohol. The most effective of these are acamprosate and naltrexone. Several other medications are currently being assessed for use in the treatment of alcohol dependence. One of the most promising of these is topiramate, a new antiepileptic drug. The main rationale for using anticonvulsants in the treatment of abuse patients is their lack of addiction potential and their role in suppressing kindling mechanisms of withdrawal (Zullino et al., 2004). It is believed that topiramate is effective in alcoholism treatment but only limited research on use of topiramate for alcohol dependence has been presented so far. Topiramate has been shown to be effective against tonic–clonic seizures in alcohol withdrawal syndrome (Rustembegovic et al., 2002). In subsequent laboratory tests, it has been shown to attenuate withdrawal signs in kindling models of ethanol dependence in rats (Cagetti et al., 2004), as well as reduce the ethanol preference in C57BL/6J mice in a free-choice study (Gabriel and Cunningham, 2005). A randomized, double-blind controlled trial has confirmed the effectiveness of topiramate compared with placebo for reducing incidences of heavy drinking in topiramate-treated alcohol-dependent patients (Johnson et al., 2004).

Preliminary studies have indicated that topiramate is effective for the treatment of post-traumatic stress disorder (PTSD) (Berlant and van Kammen, 2002). Experimental studies have confirmed the efficacy of topiramate in an animal model of PTSD (Khan and Liberzon, 2004). The traumatic events that trigger the condition lead to increases in the beta-endorphin plasma level. After trauma, the level of this peptide, which is

* Corresponding author.
E-mail address: jzalewska@pharm.am.lodz.pl (J. Zalewska-Kaszubska).

0278-5846/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2006.12.002

increased at the beginning of stress, gradually reduces and can become deficient (Volpicelli et al., 1999). It has been suggested that chronic beta-endorphin depletion may have a role in pathogenesis and continuation of PTSD (Hoffman et al., 1989).

Beta-endorphin is known to have a key role in a mesolimbic reward system, and reduced levels of this peptide may be partially responsible for drug craving and physical withdrawal symptoms (Kiefer et al., 2002; Zalewska-Kaszubska and Czarnecka, 2005).

Deficiency of this peptide was observed in people with high family risk of alcoholism (Gianoulakis et al., 1989) as well as in alcohol-preferring rats (Zalewska-Kaszubska et al., 2005). In our earlier studies, we observed a difference between the beta-endorphin levels in rats selectively bred for preference (Warsaw High Preferring; WHP) and bred for non-preference for alcohol (Warsaw Low Preferring, WLP) (Zalewska-Kaszubska et al., 2005).

Based on the beta-endorphin deficiency associated with PTSD and alcoholism, as well as the effectiveness of topiramate in the treatment of these conditions, the aim of this study was to investigate the effect of repeated topiramate treatment on beta-endorphin plasma levels. The current study examined the effect of topiramate treatment on the preferring (WHP) and non-preferring alcohol (WLP) rats, and the effect of a single application of alcohol to topiramate-treated rats of each type.

2. Materials and methods

2.1. Animals

The experiments were carried out on female adult rats from the $F_{34–36}$ generation of the WHP and WLP rat lines, which weighed 220–270 g and were kept under standard laboratory conditions. Forty-eight rats were divided into eight groups, with six animals in each group. Four groups consisted of WHP rats (24 animals) and four groups of WLP rats (24 animals). Two of the WHP groups (12 animals) and two of the WLP groups (12 animals), intragastrically received topiramate suspended in 1% methylcellulose for 14 days (80 mg/kg; 0.2 ml/100 g body weight, daily). Before a blood collection, six rats from the WHP group and six rats from WLP group were injected with ethanol, whereas the remaining six WLP and six WHP rats were injected with the same volume of saline. The other 24 rats (12 WHP and 12 WLP rats) had been treated for 14 days with the same volume of 1% methylcellulose only, and before a blood sample was collected they received an injection of ethanol or saline in the same way as the topiramate-treated rats.

All experimental procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals and were approved by the local Animal Research Committee.

2.2. Materials

Sep-pak C18 cartridges were obtained from Waters, (M.A. USA; cat. No. WAT 020515). Acetone (HPLC grade) and trifluoroacetic acid (HPLC grade) were from Baker. Aprotinin (Trascolan®) was purchased in Jelfa, Poland. Topiramate (Topamax®) was from Cilag. Ether was purchased in PoCh, Poland. The plasma beta-endorphin radioimmunoassay kit was obtained from Phoenix Pharmaceuticals, Inc., USA.

2.3. Blood sample procedure

Twenty-four hours after the last administration of topiramate or 1% methylcellulose the rats were anaesthetized with ether and blood samples were collected by heart puncture. The rats were injected with ethanol (20% w/v; 2 g/kg/10 ml) or the same volume of saline 1 hour before blood sample collection.

Blood samples were collected in tubes containing EDTA (1.6 mg/ml) and gently rocked several times to prevent coagulation. Afterwards, the samples were transferred to centrifuge tubes containing aprotinin (500 KIU/ml) and gently rocked several times to inhibit proteinase activity. The samples were then cooled in an ice-bath. The plasma was separated by centrifugation at 1600 ×*g* for 15 min at 4 °C. The plasma was frozen and stored at −20 °C until assessment.

2.4. Solid phase extraction of peptides from plasma

Plasma beta-endorphin levels were determined after extraction by the acid–acetone method. The procedure for beta-endorphin extraction used Sep-pak C18 cartridges, according to the method by Angwin and Barchas (1982) and modified by Zalewska-Kaszubska and Obzejta (2004).

Before loading on Sep-Pak C18 cartridges, plasma in 2-ml volumes was acidified in the same volume of 1% trifluoroacetic acid (TFA) and centrifuged at 10000 ×*g* for 20 min at 4 °C. C18 Sep-columns were activated by passing 2 ml of

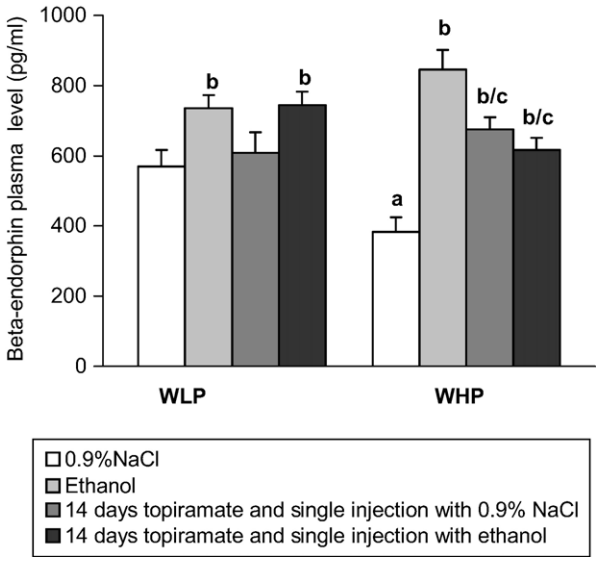

Fig. 1. Effect of single injection of ethanol (2 g/kg) on beta-endorphin plasma level in low (WLP) and high preferring rats (WHP) after 14 days administration of topiramate. Values are expressed as the mean ± SEM in each group of 6 rats. a — $P<0.05$ in comparison to WLP group injected with 0.9% NaCl; b — $P<0.05$ in comparison to adequately WLP or WHP group injected with 0.9% NaCl; c — $P<0.05$ in comparison to WHP rats injected with ethanol.