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Differential effects of low and high doses of topiramate on consolidation and retrieval of novel object recognition memory in rats

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Abstract

Topiramate is a new antiepileptic drug proposed to facilitate synaptic inhibition and block excitatory receptors. However, little is known about the effects of topiramate on memory. In the first experiment, intraperitoneal injection of topiramate at doses of 10.0 and 100.0 mg/kg, immediately after training, induced a deficit in short-term memory (STM) of a novel object recognition (NOR) task tested 1.5 hours after training in rats. In a long-term memory (LTM) test given to the same rats 24 hours after training, topiramate 0.1 mg/kg enhanced, whereas 10.0 and 100.0 mg/kg impaired, NOR retention. In the second experiment, administration of topiramate 0.01 and 0.10 mg/kg 1 hour prior to the LTM retention test improved NOR retention, whereas 10.0 and 100.0 mg/kg produced retrieval deficits. The results indicate that low doses of topiramate improve, whereas high doses impair, consolidation and retrieval of recognition memory in rats.

Keywords: Topiramate; Anticonvulsant drugs; Epilepsy; Memory consolidation; Memory retrieval; Object recognition; Recognition memory

1. Introduction

There has been growing interest in the use of new antiepileptic drugs in the treatment of epilepsy and indications other than epilepsy, including migraine prophylaxis, neuropathic pain syndromes, and neuroprotection (for recent reviews, see [1–5]). Proposed molecular mechanisms of action of new antiepileptic drugs include stimulation of the GABAergic system, inhibition of glutamate receptor-gated channels, and blockade of voltage-gated ion channels [3]. Topiramate is a new antiepileptic agent initially introduced for the management of partial seizures and approved worldwide for the treatment of several types of epilepsy. Topiramate has also been proposed as a therapeutic agent for other neurological and psychiatric disorders including migraine [2,4–9].

Patients with epilepsy may have impaired cognitive abilities, and antiepileptic drug therapy may contribute to this impairment [10,11]. Several reports have suggested that newer antiepileptic drugs such as topiramate have fewer effects on cognition than older drugs [12–14]. Thus, assessment of the potential adverse cognitive effects of new antiepileptic drugs using animal models may have implications for the clinical use of topiramate in the treatment of epilepsy and other conditions such as migraine. For instance, topiramate has been reported to produce a dose-related impairment in working memory assessed by spatial alternation behavior in rats [15]. Although antiepileptic drugs can impair neuropsychological functioning, their positive effect on seizure control may improve cognition and behavior. In addition, topiramate was reported to enhance performance

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in a water maze in sham- but not brain-injured animals [16].

As mentioned above, proposed mechanisms mediating the actions of topiramate include sodium channel blockade; positive modulation of γ-aminobutyric acid (GABA) type A ($GABA_A$) receptors; and inhibition of the aminohydroxymethylisoxazole propionic acid (AMPA) and kainate non-*N*-methyl-D-aspartate (NMDA) glutamate receptor subtypes [1,3,4,6,17–19]. GABA and glutamate receptors and sodium channels have been implicated in memory formation and recall.

The novel object recognition memory (NOR) task is based on the spontaneous tendency of rodents to explore a novel object in preference to a familiar object. It is a nonspatial and non-rewarded task that might depend on both the hippocampus and the nigrostriatal dopaminergic pathway [20–22]. Studies performed by Winters and Bussey [23–25] have indicated participation of the perirhinal cortex in recognition memory and have suggested that, as in the hippocampus, AMPA and NMDA glutamate receptors mediate synaptic transmission and activity-dependent synaptic plasticity, respectively, in several stages of memory processing (encoding, retrieval, and consolidation). Thus, the NOR procedure may be a useful preclinical model with which to characterize the effects of new antiepileptic drugs on cognitive function. The aim of the present study was to evaluate the effects of topiramate on consolidation and retrieval of NOR. The first experiment examined the effects of topiramate on consolidation in rats systemically administered topiramate immediately after NOR training. A second experiment examined the effects of topiramate on retrieval in animals given topiramate 1 hour before an NOR 24-hour retention test trial.

2. Method

2.1. Subjects

Adult female Wistar rats were obtained from the State Health Research Foundation (FEPPS-RS, Porto Alegre, Brazil). The rats were maintained in groups of five animals in a plastic cage with sawdust bedding at a room temperature of 22 ± 1 °C and on a 12-hour light/12-hour dark cycle. The animals were supplied with standardized pellet food and tap water ad libitum. Behavioral testing started when animals reached the age of 3 months. All experimental procedures were performed in accordance with the *NIH Guide for Care and Use of Laboratory Animals* (NIH Publication No. 80-23 Revised 1996).

2.2. Drugs and injection procedures

For the first experiment, topiramate (Janssen–Cilag Pharmaceuticals, São Paulo, Brazil; 0.01, 0.1, 1.0, 10.0, or 100.0 mg/kg body weight) or saline (0.9% NaCl) was administered intraperitoneally (1.0 ml/kg injection volume) immediately after the NOR training trial. For the second experiment, topiramate (0.01, 0.1, 1.0, 10.0, or 10.00 mg/kg) or saline was administered intraperitoneally 1 hour before the NOR long-term retention test trial.

2.3. Novel object recognition

The NOR task apparatus and procedures have been described elsewhere [22,26,27]. Briefly, an open-field apparatus ($45 \times 40 \times 60$ cm) made of plywood with sawdust covering its floor was used in the NOR task. On the first day, rats were submitted to a habituation session during which they were placed in the empty open field for 5 minutes. On the following day, rats were given one 5-minute training trial in which they were exposed to two identical objects (A1 and A2). All objects were made of Duplo Lego Toys and were similar in texture, color, and size, but had distinctive shapes. The objects were positioned in two adjacent corners, 9 cm from the walls. On a short-term memory (STM) retention test trial given 1.5 hour after the training session, rats were allowed to explore the open field for 5 minutes in the presence of two objects: the familiar object A and a novel object B. These were placed in the same locations as in the training trial. On a long-term memory (LTM) retention test trial carried out 24 hours after the training trial, rats were allowed to explore the open field for 5 minutes in the presence of the familiar object A and a third novel object C. The same animals were used for the STM and LTM retention tests as previously described [22,26,27]. Object exploration was measured using two stopwatches to record the time spent exploring the objects during the experimental sessions. Exploration was defined as sniffing or touching the object with the nose. Sitting on the object was not considered exploration. A recognition index for each animal was calculated as the ratio $T_N/(T_F + T_N)$, where T_F = time spent exploring the familiar object (A), T_N = time spent exploring the novel object (B or C). For the training trial, the index was the ratio of time spent exploring object A2 to time spent exploring both objects $[T_{A2}/(T_{A1} + T_{A2})]$.

2.4. Statistics

Groups were compared using Kruskal–Wallis analysis of variance followed by the Mann–Whitney *U* test when necessary. Comparisons between sessions within the same group were made using the Wilcoxon test [26,27]. *P* values less than 0.05 were considered to indicate statistical significance.

3. Results

The first experiment examined the effects of posttraining systemic administration of topiramate on consolidation of short- and long-term object recognition memory. Administration of topiramate at 10.0 and 100.0 mg/kg induced STM deficits, as recognition indexes of these groups were significantly lower than the recognition index of the saline-treated group (both P's < 0.01) (Fig. 1, top). In the LTM test, results indicated that topiramate 0.1 mg/kg induced enhancement of recognition memory ($P < 0.05$ compared with saline-treated animals), whereas topiramate 10.0 or 100.0 mg/kg caused impairment of LTM (both P's < 0.01 compared with saline-treated animals) (Fig. 1, bottom). Moreover, statistical analysis comparing recognition indexes obtained in training and long-term retention sessions within groups indicated that the group that received the highest dose of topiramate (100.0 mg/kg) had a complete memory blockade, as the animals showed no significant preference toward the novel object in the testing session ($P = 0.17$). There was no significant difference among groups in the total time spent exploring both objects during the training trial: mean ± SE time spent exploring both objects was 24.1 ± 4.6 in the saline-treated group, 20.7 ± 3.8 in the group treated with topiramate