Effects of some convulsant agents on the protective activity of topiramate against maximal electroshock-induced seizures in mice

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Abstract:
The anticonvulsant activity of topiramate combined with some convulsant agents (bicuculline – BIC, N-methyl-D-aspartate – NMDA, and kainic acid – KA), given at subconvulsive doses, was evaluated in the maximal electroshock (MES)-test in mice. BIC (1.5 mg/kg), KA (10 mg/kg) and NMDA (50 mg/kg) significantly decreased the anticonvulsant activity of topiramate raising its ED₉₀ from 76.2 mg/kg to 135, 102, and 107 mg/kg, respectively. BIC (0.75 mg/kg) and KA (5 mg/kg) did not alter the protective activity of topiramate in the MES-test. Moreover, topiramate injected alone (up to 135 mg/kg) did not affect motor performance and long-term memory of animals tested in the chimney and passive avoidance tests, respectively. In contrast, combinations of topiramate with BIC (1.5 mg/kg), NMDA (50 mg/kg) or KA (10 mg/kg) considerably disturbed long-term memory in mice. Additionally, co-administration of topiramate with KA (10 mg/kg) or BIC (1.5 mg/kg) significantly impaired motor performance, whereas topiramate co-administered with NMDA (50 mg/kg) had no impact on motor coordination in mice. None of the studied convulsants affected the free plasma concentration of topiramate assayed with immunofluorescence method. The results of this study seem to indicate the expression of the anticonvulsant activity of topiramate is dependent on all ionotropic glutamate and GABA receptor-mediated events.

Key words:
topiramate, N-methyl-D-aspartate, kainate, bicuculline, maximal electroshock-induced seizures

Introduction

There is no doubt that excitatory amino acids (glutamate and aspartate) play an important role in the initiation of seizures [12]. This phenomenon usually occurs after the activation of NMDA (N-methyl-D-aspartate) and/or α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid (AMPA)/kainate (KA) receptors (all three subtypes are classified as ionotropic glutamate receptors). Another mechanism contributing to seizure initiation involves an inhibition of γ-aminobutyric acid (GABA)ergic neurotransmission. In experimental and biochemical studies, it has been found that NMDA, AMPA and KA as well as agents blocking GABA_A receptor-mediated neurotransmission are potent convulsants [10]. For instance, bicuculline (BIC) is an experimental substance widely used for inducing seizures through the inhibition of GABA_A receptors [21]. In contrast, NMDA and AMPA/KA receptor antagonists markedly suppressed