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Effect of three glutamatergic metabotropic receptor ligands on electrically-induced seizures in mice

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Abstract: The objective of this study was to determine whether the effect of 3 agonists of glutamatergic metabotropic receptors (mGluRs): ACPT, DCPG, MTPG. ACPT and DCPG (agonists of mGluR III receptors) administered at the dose of 20 mg/kg increased the electroconvulsive threshold in mice. In contrast, MTPG, an agonist of mGluR II and mGluR III receptors, applied at the same dose (20 mg/kg) significantly decreased the threshold, presenting proconvulsant action. This surprising effect may be due to agonistic properties of MTPG towards mGluR II receptors.

Key words: glutamatergic receptors, metabotropic receptors, electroconvulsions

INTRODUCTION

Glutamatergic metabotropic receptors may be divided in 3 groups, depending on their pharmacological properties. Activation of group I receptors (mGluR I) increases activity of phospholipase C, while receptors belonging to group II (mGluR II) or group III (mGluR III) are negatively coupled with adenylyl cyclase. Receptors of all groups are implicated in the modulation of seizure phenomena [1].

(1S,3R,4R)-Aminocyclopentan-1,3,4-tricarboxylate (ACPT-1) is an agonist mGluR 4α belonging to mGluR III autoreceptors. The main pharmacological action of ACPT is therefore the inhibition of glutamate release [2]. 3,4-Dicarboxyphenylglycine (DCPG) is a selective agonist of mGluR 8 (mGluR III), antagonist of glutamatergic ionotropic AMPA, and, weakly, NMDA receptors [3]. It was reported that *i.c.v.* administration of ACPT or DCPG abolished audiogenic seizures in mice [4]. On the other hand, (R,S)-α-methyl-tetrazolphenylglycine (MTPG) is a nonselective agonist of mGluR II and, to a lesser degree, of mGluR III receptors [5].

All 3 mGluR agonists described may open a new avenue in pharmacological science as valuable targets for drug therapy in epilepsy [6]. Therefore, we decided to examine the influence of ACPT, DCPG and MTPG on the electroconvulsive threshold in mice, one of the basic experimental models for tonic-clonic convulsions.

MATERIALS AND METHODS

Animals. All experiments were performed on male Swiss mice, kept in colony cages with free access to food and tap water, under standardized housing conditions. The animals were randomly assigned to experimental groups consisting of 8 mice. Each mouse participated in only 1 experiment. All tests were performed between 09:00-14:00 p.m. to minimize confounding effects of circadian rhythms. All experimental procedures were approved by the Local Ethics Committee at the Medical University in Lublin.

Drugs. (1S,3R,4R)-Aminocyclopentan-1,3,4-tricarboxylate (ACPT), 3,4-dicarboxyphenylglycine (DCPG), and (R,S)-α-methyl-tetrazolphenylglycine (MTPG) (all 3 drugs obtained from Tocris Ltd, UK) were suspended in a 1% solution of Tween 80 (Sigma St. Louis, MO, USA). All drugs were administered *i.p.*, ACPT-1 30 min, and DCPG and MTPG 15 min before the electroconvulsive threshold test.

Electroconvulsions. Electroconvulsions were induced by using alternating current (50 Hz) produced by a Rodent Shocker Generator (Ataner, Lublin, Poland), and delivered by ear-clip electrodes. The stimulus duration was 0.2 s. The electroconvulsive threshold (CS_{50}) was the strength of current (in mA) necessary to produce tonic hindl imb extension in 50% of the animals tested. In order to evaluate CS_{50}s at least 4 groups consisting of 8 mice each were used. Subsequently, an intensity-response curve was constructed, based on the percentage of convulsing mice.

Statistics. Statistical analysis of the data obtained was undertaken by computer probit analysis, according to Litchfield and Wilcoxon [7].

RESULTS

Effect of ACPT on the electroconvulsive threshold. ACPT-1 (at the dose of 2 and 10 mg/kg) did not affect the electroconvulsive threshold, while when applied at 20 mg/kg, it significantly raised this parameter (Fig. 1).

Effect of DCPG on the electroconvulsive threshold. DCPG (applied at 2 and 10 mg/kg) did not change the threshold. The drug administered at 20 mg/kg significantly raised the electroconvulsive threshold in mice (Fig. 2).

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Effect of MTPG on the electroconvulsive threshold. MTPG (at 2 and 10 mg/kg) did not affect the threshold in mice, but when applied at 20 mg/kg, it decreased the value of this parameter (Fig. 3).

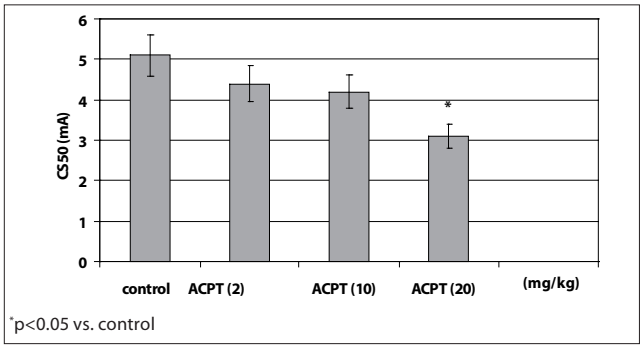

Figure 1 Influence of ACPT on electroconvulsive threshold in mice. CS50 (in mA) is the strength of current producing tonic convulsions in 50% of animals.

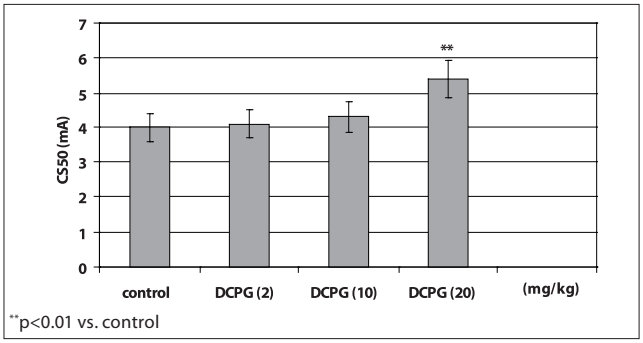

Figure 2 Influence of DCPG on electroconvulsive threshold in mice. CS50 (in mA) is the strength of current producing tonic convulsions in 50% of animals.

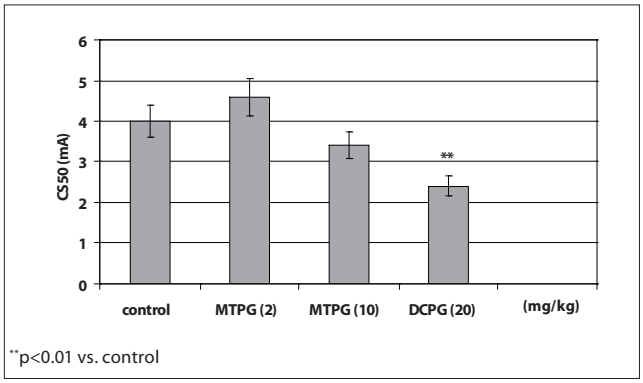

Figure 3 Influence of MTPG on electroconvulsive threshold in mice. CS50 (in mA) is the strength of current producing tonic convulsions in 50% of animals

DISCUSSION

The results obtained demonstrate that all 3 agonists of mGluR receptors exhibited anticonvulsant properties, increasing the electroconvulsive threshold in mice. There is evidence that a variety of mGluR III agonists may present antiseizure action in the model of audiogenic convulsions in mice [4]. This effect was partially reversed by mGluR III antagonists, including (R,S)-α-methylserine-O-phosphate [8]. The beneficial action of ACPT and DCPG in audiogenic seizures may be associated with localization of mGluR4α and mGluR8 receptors in the inferior tegmental colliculi [4]. However, the proconvulsive action of MPTG was quite surprising, the more the substance was effective in seizures induced by homocysteic acid in immature rats [9]. This phenomenon could be related to the agonistic action of MPTG towards receptors of mGluR II group. Nevertheless, mGluR II and mGluR III are the least examined of all metabotropic receptors. To date, most investigations have employed receptors of mGluR I group. Moldrich et al. [6] found that their agonists enhanced chemically-evoked convulsions, whereas their antagonists inhibited comvulsions. The antagonist of mGluR1 receptors, LY 367385, and the antagonist of mGluR5 receptors (MPEP) attenuated pentylenetetrazole-induced convulsions in mice [10]. MPEP raised the electroconvulsive threshold, but remained without effect on the protective activity of conventional antiepileptic drugs, including, valproate, carbamazepine, phenytoin, and phenobarbital [10].

CONCLUSIONS

1. Agonists of mGluR III receptors may present anticonvulsant action in the model of electroconvulsive threshold in mice.
2. Proconvulsant effect of MTPG may be dependent on its agonistic activity on mGluR II receptors.
3. Further investigations, including interactions with antiepileptic drugs, are needed for evaluation of the usefulness of such agonists in additive treatment of seizures.

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