POTENTIAL ANTIPSYCHOTIC AND EXTRAPYRAMIDAL EFFECTS OF (R,S)-3,4-DICARBOXYPHENYLGLYCINE [(R,S)-3,4-DCPG], A MIXED AMPA ANTAGONIST/mGluR8 AGONIST

Krystyna Ossowska, Małgorzata Pietraszek, Jadwiga Wardas, Stanisław Wolforth

Department of Neuro-Psychopharmacology, Institute of Pharmacology, Polish Academy of Sciences, Sienkiewicza 2, PL-31-343 Kraków, Poland


An involvement of glutamatergic transmission in schizophrenia has been postulated for several years. According to that view, hypofunction of NMDA receptors and a compensatory increase in glutamate release which overstimulates non-NMDA receptors contributes to psychotic symptoms. Therefore, potential antipsychotic drugs are searched for among compounds which block AMPA receptors and inhibit glutamate release. (R,S)-3,4-dicarboxyphenylglycine [(R,S)-3,4-DCPG] is a mixed antagonist of AMPA receptors and agonist of an autoreceptor, i.e. metabotropic glutamate receptor 8. The aim of the study was to look for putative antipsychotic properties of (R,S)-3,4-DCPG in the model of locomotor stimulation induced by amphetamine or phencyclidine in mice. Moreover, a risk of extrapyramidal side-effects induced by this compound was examined, as capability to induce catalepsy in the bar test and to increase the proenkephalin mRNA expression, measured autoradiographically in striatal slices by in situ hybridization. (R,S)-3,4-DCPG (80 mg/kg ip) decreased the amphetamine (2.5 mg/kg sc)-but not phencyclidine (3 mg/kg sc)-induced hyperactivity. That dose of (R,S)-3,4-DCPG did not decrease the spontaneous locomotor activity of mice. However, a dose of 100 mg/kg ip of that compound evoked catalepsy and enhanced the catalepsy and striatal proenkephalin mRNA expression induced by haloperidol (1–2 mg/kg ip). The study seems to suggest that (R,S)-3,4-DCPG may possess antipsychotic properties at doses close to those evoking extrapyramidal side-effects which speaks for its rather typical than atypical neuroleptic profile.

Key words: (RS)-3,4-dicarboxyphenylglycine, AMPA receptor, metabotropic glutamate receptor 8, neuroleptic, amphetamine-induced hyperlocomotion, phencyclidine-induced hyperlocomotion, catalepsy, proenkephalin mRNA, striatum, mice

# correspondence: e-mail: ossowska@if-pan.krakow.pl