Anxiolytic-like effects of group III mGlu receptor ligands in the hippocampus involve GABA<sub>A</sub> signaling

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Abstract:
Recent literature data and the results of our earlier pharmacological studies, have provided evidence that antagonists of group I metabotropic glutamate receptors (mGluRs) and agonists of group II mGluRs show anxiolytic-like properties in preclinical and clinical studies. Out of all glutamate receptors, the role of group III mGluRs in anxiety-like states is the least investigated because of the lack of specific pharmacological tools, moreover all group III receptor ligands synthesized so far are not systemically active, so they have to be administered centrally. In the present study, we investigated the anxiolytic-like activity of group III mGlu receptor ligands including a nonselective group III mGlu receptor agonist (1S,3R,4S)-1-aminocyclopentane-1,3,4-tricarboxylic acid (ACPT-I), group III mGlu receptor antagonist, (RS)-3-cyclopropyl-4-phosphonophenylglycine (CPPG) and a positive allosteric modulator of mGluR4 (-)-N-phenyl-7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxamide (PHCCC). The Vogel conflict drinking test in rats was used to test the anxiolytic-like effects. The hippocampus was chosen as a site of the injection of drugs, as this brain regions is involved in the regulation of anxiety-related behavior. Intrahippocampal injections (CA1 region of the hippocampus) of PHCCC (12 nmol) but not of CPPG (75 nmol) produced an anxiolytic-like response, moreover, the effect of PHCCC was totally blocked by CPPG. The anxiolytic-like effects of ACPT-I (7.5 nmol) or PHCCC (12 nmol) were significantly attenuated by flumazenil (10 mg/kg), indicating an involvement of GABAergic system in the anxiolytic-like response.

Key words:
ACPT-I, CPPG, PHCCC, anxiety, conflict drinking test, group III mGlu receptors