Publication

Anxiolytic-like effects of the prototypical metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl) pyridine in rodents.

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Abstract

Recently, selective and systemically active antagonists for the metabotropic glutamate 5 receptor (mGlu(5)) were discovered, and the most potent derivative was found to be MPEP (2-methyl-6-(phenylethynyl)pyridine). Given the high expression of mGlu(5) receptors in limbic forebrain regions, it was decided to evaluate the anxiolytic potential of MPEP. After an acute oral administration, MPEP attenuated the anxiety-dependent variable in a variety of well established anxiety test paradigms. In rats, MPEP (10, 30, and 100 mg/kg) increased punished responses in the Geller-Seifter test, but none of these effects reached statistical significance. MPEP significantly increased the ratio (open/total arm entries; 0.1, 1, and 10 mg/kg), the number of open arm entries (0.1, 1, and 10 mg/kg), as well as time spent on open arm (0.1 and 1 mg/kg) in the elevated plus maze test. Furthermore, MPEP (0.3 and 1 mg/kg) significantly increased the time spent in social contact in the social exploration test. In mice, MPEP attenuated stress-induced hyperthermia (15 and 30 mg/kg) and decreased the number of buried marbles in the marble burying test (7.5 and 30 mg/kg). Finally, MPEP (0.01, 0.1, 1, 10, and 100 mg/kg) was tested on spontaneous locomotor activity in mice, and only a dose of 100 mg/kg significantly reduced vertical activity; no effect was seen on horizontal activity. MPEP (7.5, 15, and 30 mg/kg) was ineffective on d-amphetamine-induced (2.5 mg/kg) locomotor activity in mice and prepulse inhibition in rats (1, 3, or 10 mg/kg). Thus, these findings indicate that MPEP exhibits anxiolytic-like effects and low risks for sedation and psychotomimetic side-effects in rodents.