Evaluation of antipsychotic properties of M₄ muscarinic acetylcholine receptor agonists in mice

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M₁ and/or M₄ muscarinic acetylcholine receptors are suggested to be involved in the pathogenesis and treatment of schizophrenia. To validate the antipsychotic potential of M₄ receptor activation, we evaluated the antipsychotic properties of the selective M₄ agonist (Compound **1**, Bioorg. Med. Chem. Lett., 24, 2909, 2014) in mice and compared them to those of xanomeline (M₁/M₄ preferring agonist). Apomorphine (APO, 4 mg/kg, s.c.)-induced hyperactivity test was used for the evaluation of antipsychotic activity and pole-test for the assessment of extrapyramidal side effects (bradykinesia). Treatment of animals with Compound **1** (0.3-3 mg/kg, s.c.) significantly inhibited APO-induced hyperactivity in a dose-dependent manner. Compound **1** did not induce bradykinesia at higher doses (1-10 mg/kg, s.c.), and it rather tended to reduce haloperidol (1 mg/kg, i.p.)-induced bradykinesia. Meanwhile, xanomeline (1-10 mg/kg, s.c.) also inhibited APO-induced hyperactivity, but it was 3 times less potent than Compound **1**. In addition, xanomeline induced bradykinesia at 3-10 mg/kg and muscle relaxation at 10-30 mg/kg (s.c.). Our results suggest that activation of M₄ receptors is linked to the antipsychotic activity and is more promising than the mixed M₁/M₄ receptor activation.