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Protective Effect of the Histamine H3 Receptor Antagonist DL77 in Behavioral Cognitive Deficits Associated with Schizophrenia

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Abstract : The effects of the non-imidazole histamine H3 receptor (H3R) antagonist DL77 in passive avoidance paradigm (PAP) and novel object recognition (NOR) task in MK801-induced cognitive deficits associated with schizophrenia (CDS) in adult male rats, and applying donepezil (DOZ) as a reference drug were investigated. The results show that acute systemic administration of DL77 (2.5, 5, and 10 mg/kg, i.p.) significantly improved MK801-induced (0.1 mg/kg, i.p.) memory deficits in PAP. The ameliorating activity of DL77 (5 mg/kg, i.p.) in MK801-induced deficits was partly reversed when rats were pretreated with the centrally-acting H2R antagonist zolantidine (ZOL, 10 mg/kg, i.p.) or with the antimuscarinic antagonist scopolamine (SCO, 0.1 mg/kg, i.p.), but not with the CNS penetrant H1R antagonist pyrilamine (PYR, 10 mg/kg, i.p.). Moreover, the memory enhancing effect of DL77 (5 mg/kg, i.p.) in MK801-induced memory deficits in PAP was strongly reversed when rats were pretreated with a combination of ZOL (10 mg/kg, i.p.) and SCO (1.0 mg/kg, i.p.). Furthermore, the significant ameliorative effect of DL77 (5 mg/kg, i.p.) on MK801-induced long-term memory (LTM) impairment in NOR test was comparable to the DOZ-provided memory-enhancing effect, and was abrogated when animals were pretreated with the histamine H3R agonist R-(α)-methylhistamine (RAMH, 10 mg/kg, i.p.). However, DL77(5 mg/kg, i.p.) failed to provide procognitive effect on MK801-induced short-term memory (STM) impairment in NOR test. In addition, DL77 (5 mg/kg) did not alter anxiety levels and locomotor activity of animals naive to elevated-plus maze (EPM), demonstrating that improved performances with DL77 (5 mg/kg) in PAP or NOR are unrelated to changes in emotional responding or spontaneous locomotor activity. These results provide evidence for the potential of H3Rs for the treatment of neurodegenerative disorders related to impaired memory function, e.g. CDS.

Keywords : histamine H3 receptor, antagonist, learning, memory impairment, passive avoidance paradigm, novel object recognition
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