Detrimental effect of postnatal blockade of N-methyl-D-aspartate receptors on sensorimotor gating is reversed by neuroleptic drugs

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Abstract:

Postnatal hypofunction of N-methyl-D-aspartate (NMDA) receptors leads to several behavioral deficits in adult rats resembling deficits typical of schizophrenia-like deficits of sensorimotor gating. Thus far, it is not known whether the above disruptions are sensitive to neuroleptic drugs. In order to verify the above model in pharmacological terms, we investigated whether deficits in the sensorimotor gating evoked by administration of NMDA receptor antagonists in the postnatal period is sensitive to neuroleptic drugs. We also investigated whether such treatment evoked alterations in the expression of dopamine D₁, D₂ and D₃ receptors in the nucleus accumbens, a key structure for dopamine-dependent alterations in sensorimotor gating. CGP 40116, a competitive antagonist of NMDA receptors was given in doses of 1.25 mg/kg on days 1, 3, 6 and 9; 2.5 mg/kg on days 12, 15 and 18; and 5 mg/kg on day 21 (all injections were sc). The efficacy of sensorimotor gating was tested on rats at the age of 60 days using a prepulse-induced inhibition of the startle reflex. In order to measure the expression of dopamine D₁, D₂ and D₃ receptors, we used quantitative autoradiography and tritiated ligands i.e. [³H]-SCH 23390, [³H]-Spiperone and [³H]-7-OH-DPAT, respectively. Haloperidol (0.1 mg/kg, sc), risperidone (1.0 mg/kg, sc) and clozapine (2.5 mg/kg, sc) reversed deficits of sensorimotor gating observed in adult rats evoked by the postnatal administration of CGP 40116. We also observed enhanced density of dopamine D₃, but not D₁ and D₂ receptors in the nucleus accumbens of CGP 40116 treated rats. It is concluded that models of cognitive dysfunction, typical for schizophrenia based on postnatal administration of NMDA receptor antagonists, are sensitive to neuroleptic drugs and possibly not dependent on alteration in the density of dopaminergic receptors.

Key words:

developmental model of schizophrenia, NMDA receptors, sensorimotor gating, neuroleptic drugs