

The role of allosteric modulation of mGluR on behavioral changes induced by ketamine model of schizophrenia

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Introduction. Schizophrenia is a mental disorder characterized by a disintegration of the process of thinking and of emotional responsiveness. It has been suggested that specific neurochemical abnormality associated with schizophrenia is due to dopaminergic overactivity in the brain. Schizophrenia is currently thought to be associated with a hypoglutamatergic state. Taken into consideration the role of glutamatergic system in development of schizophrenia and involvement of striatal dopaminergic receptors in generation of schizophrenia symptoms, it was planned to study the functional interaction between NMDA and metabotropic glutamatergic receptors 5 (mGluR5) in schizophrenia-associated behavioral and memory disturbance and the role of mGluRs allosteric modulation in cortico-striatal synaptic plasticity.

Methods. Behavioral experiments. Rat model of schizophrenia were induced by low doses of non-competitive antagonist of glutamatergic NMDA-receptors ketamine (0.3-0,5mg/kg. i.p.). Schizophrenia model-associated behavioral changes were monitored in the open-field, T-maze test and passive avoidance task.

Results. In our experiments investigation of dose-dependent effects of ketamine revealed that 0.3mg/kg ketamine induces statistical changes in most of behavioral and cognitive parameters. Alterations in emotional state showed decrease of the number and total duration of grooming in behavioral experiments. Decrease of motor activity was also detected, statistical changes were observed in number of defecations and urination. In T-maze test it was shown that spatial memory was damaged. To determine whether mGlu5 and NMDA receptor interact to regulate complex behaviors that are relevant to cognitive disorders such as schizophrenia we focused on assessing whether the selective mGlu5 receptor antagonist 2-methyl-6-(phenylethynyl)-pyridine MPEP mimics or exacerbates the effects of the NMDA receptor antagonist. Ketamine-induced memory disturbance was significantly increased after injection of mGluR5 negative allosteric modulators MPEP.

In *in vivo* experiments effects of antipsychotic drugs (haloperidol and clozapine) on ketamine-induced cognitive and emotional changes were studied. In our experiments Haloperidol (0.2mg/kg) and clozapine (1.3mg/kg) wasn't effective to correct the memory disturbance and the changes in emotional status induced by Ketamine injection.

Comparative analyses with positive allosteric modulator DFB (3,3-Difluorobenzaldazine) was performed. The analyses show that DFB (1mg/kg) has corrects emotional disturbances in schizophrenia model unlike above-mentioned antipsychotics. But it wasn't effective to correct the memory disturbance induced by ketamine.

Conclusion. Due to our behavioral experiments it was suggested that during some neurological or psychiatric disorders with NMDA dysfunction pharmacological manipulation of mGlu5 receptors could have therapeutic effects.