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ROLE OF 5-HT2A AND MGLU2 AS A GPCR HETEROCOMPLEX IN ANTIPSYCHOTIC ACTION

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The serotonin (5-HT) and glutamate (Glu) neurotransmitter systems are suspected in the etiology and pathophysiology of schizophrenia, as well as in the mechanism of action of antipsychotic drugs. A high affinity for the serotonin 5-HT_{2A} receptor is a common characteristic of all atypical antipsychotics. Hallucinogenic 5-HT_{2A} agonists, such as lysergic acid diethylamide (LSD) or psilocybin, produce psychosis-like syndrome in humans that resembles the first episodes of schizophrenia. In addition, in recent clinical studies, a metabotropic glutamate 2/3 (mGlu2/3) receptor agonist has shown promise as a new treatment for schizophrenia. We show that 5-HT_{2A} and mGlu2 receptors form a specific G protein-coupled receptor (GPCR) heteromeric complex through which serotonin and glutamate elicit a unique pattern of G protein coupling in living cells. Our findings suggest that the 5-HT^{2A}-mGlu2-mediated changes in Gq and Gi activity predict the psychoactive behavioral effects of a variety of pharmacological compounds, including antipsychotic and hallucinogen. These observations provide a molecular mechanistic insight into antipsychotic action.

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