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### The antipsychotic activity of mGlu receptor agents, focus on novel allosteric vs. orthosteric agonists of mGlu4 receptors

Modulation of the glutamatergic system via metabotropic glutamate receptors (mGlu) including mGlu5 receptor, positive allosteric modulators (PAMs) and mGlu2/3 receptor stimulators which could be a new, efficient way to achieve antipsychotic-like effects. The metabotropic glutamate 4 (mGlu4) receptor is the most studied among group III mGlu receptors. The antipsychotic activity of the non-selective orthosteric agonist of mGlu<sub>4</sub>/mGlu<sub>8</sub> receptors, ACPT-I was demonstrated. The activity of the compound was evident in the models' predictive of positive symptoms, moreover, it was shown that ACPT-I dose-dependently inhibited spontaneous EPSC evoked by DOI administration in rat frontal cortex. Similar results were obtained for the second orthosteric agonist of mGlu receptors, LSP1-2111. Later on it was shown that the compound also possessed activity towards negative and cognitive symptoms of schizophrenia, measured in the social interaction and novel object recognition tests. Similar results were obtained with selective mGlu4 receptor PAMs Lu AF21934 or ADX88178. These compounds showed an antipsychotic-like activity in animal models, albeit the efficacy of the former compound was stronger than that for the latter one. The actions of Lu AF21934 were robust and evident in animal models of positive, negative and cognitive symptoms. The administration of the selective 5-HT<sub>1A</sub> antagonist WAY100635 fully reversed the action of both LSP1-2111 (orthosteric agonist) and Lu AF21934 (positive allosteric modulator) in preclinical models considered as mirroring positive, negative and cognitive symptoms of schizophrenia. Simultaneously, the administration of sub-effective doses of the ligands induced clear antipsychotic-like effects not observed for each compounds separately. Therefore it can be speculated that the combined treatment based on the mGlu<sub>4</sub>-5-HT<sub>1A</sub> agonism may be regarded as a potentially effective new antipsychotic treatment.

### Biography

Andrzej Pilc, MD, PhD is now the Head of Neurobiology Department at the Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland. His main research interest is in the studies of the mechanism of action of antidepressant/anti-anxiety/antipsychotic drugs including the involvement of mGlu or GABA<sub>B</sub> receptor ligands. He is a principal investigator in a number of grants, received several national awards and is one of the most frequently cited Polish pharmacologists.

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