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FUNCTIONAL ANALYSIS OF DRUG–RECEPTOR INTERACTION: STUDY OF CLINICALLY USED AND NOVEL ANTIPSYCHOTICS

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Objectives: Schizophrenia is a complex disorder with positive and negative symptoms and with cognitive impairments. Classical antipsychotics, the potent dopamine 2 receptor (D2R) antagonists, control positive symptoms but may cause extrapiramidal side effects. Atypical drugs with lower affinity toward D2R, obviate this problem but do not improve cognitive functions. It has been demonstrated that serotonin 6 (5-HT6R) receptor and serotonin 2A (5-HT2AR) receptor antagonists show beneficial effect on cognition in several animal models. Our study was aimed at evaluating functional activity of novel antipsychotics toward D2R, 5-HT6R and 5-HT2AR.

Methods: Six of clinically used antipsychotic drugs (haloperidol, chloropromazine, olanzapine, clozapine, risperidone, quetiapine) and 9 novel potential antipsychotics (synthesized at our institute) were assessed for their antagonistic properties. Ligands ability to decrease the serotonin-stimulated second messengers (cyclic AMP and inositol phosphates, respectively) was tested in cell lines overexpressing 5-HT6R and 5-HT2AR. The drug ability to inhibit the dopamine-activated D2R was measured in GeneBLAzer® D2-Gqo5-NFAT-*bla* CHO-K1 cells. The IC50 and antagonist/partial agonist properties were determined from dose-response curve.

Results: In our assay all tested drugs were D2R and 5-HT2AR antagonists, and except haloperidol, risperidone and quetiapine, they also attenuated 5-HT6R activity. All novel ligands were found to inhibit the activation of these three receptors.

Conclusions : All tested compounds were functionally active and modulated the receptor-actuated response of second messenger system. Further changes in a chemical structure of ligands may improve the receptor profile and their antipsychotic/ pro-cognitive abilities.

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