ANTIPSYCHOTIC EFFECT OF GLYCINE REUPTAKE INHIBITION, INDUCED BY ORG-24461 A GLYCINE TRANSPORTER-1 TYPE BLOCKER

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The dopaminergic hyperactivity theory as the neurochemical basis of schizophrenia has been generally accepted for a long time, supported by clinical observations that dopamine receptor antagonists can attenuate the symptoms of the illness. Since the discovery that phencyclydine (PCP, a non-competitive NMDA receptor antagonist) has been able to induce symptoms of schizophrenia in human patients and it can be used as „schizophrenic agent" in animal experiments, NMDA receptor hypofunction became a new theory in the pathophysiology of schizophrenia. Though potential neurotoxicity excludes the use of direct glutamatergic agonists, facilitation of glutamatergic activity can be achieved by increasing the co-agonist glycine concentration around the NMDA receptors [1]. Glycine is released from glial cells via the glycine transporter-1 (GlyT1) and specific inhibitors of GlyT-1 can increase glycine concentration in the vicinity of NMDA receptors [2]. Org-24461 is an N-methylglycine derivative of fluoxetine, synthesized conveniently in two steps starting from fluoxetine.

Org-24461 inhibited glycine reuptake in vitro in rat brain synaptosomal preparation without having affinity to serotonergic, adrenergic and dopaminergic receptors. Behavioral tests suggest its preferential effect on the negative symptoms of shizophrenia, it inhibited PCP-induced hyperlocomotion in mice, PCP-induced social withdrawal and EEG-desynchronization in rats. On the other hand, it was ineffective to alleviate positive-like symptoms, like D-amphetamine-induced hyperlocomotion or apomorphine-evoked stereotypy or climbing. These results indicate the therapeutic usefulness of GlyT-1 inhibitors in antipsychotic treatment even in the amelioration of the often therapy resistant negative symptoms of schizophrenia.

[1] Javitt DC. Glycine modulators in schizophrenia Curr Opin Invest Drugs, 2002.
[2] Harsing LG Jr. et al. The glycine transporter1 inhibitor NFPS and Org24461: a pharmacological study. Pharm Biochem Behav, 2003.