Interactions of tricyclic antipsychotic and antidepressant medications with a novel binding site in $GABA_A$ receptors

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Abstract

Background and Purpose: Many psychotherapeutic drugs including clozapine have a polypharmacological profile and act on $GABA_A$ receptors, where subtype-specific information is often lacking. Patients with schizophrenia show alterations in function, structure and molecular composition of the hippocampus, and a recent study demonstrated aberrant levels of hippocampal α5 subunit containing $GABA_A$ receptors. **Experimental Approach:** Functional studies of GABA modulatory effects by antipsychotic and antidepressant medications were performed in several $GABA_A$ receptor subtypes by two-electrode voltage-clamp electrophysiology using *Xenopus laevis* oocytes. Computational structural analysis was employed to design mutated constructs of the α5 subunit, probing a novel binding site. Computational ligand analysis complemented the functional and mutational data. **Key Results:** We show that the antipsychotic drugs clozapine and chlorpromazine have negative modulatory effects on multiple $GABA_A$ receptor subtypes, including α5-containing. On the latter we show negative modulatory effects for five additional antipsychotic and antidepressant drugs. Based on a chlorpromazine binding site observed in a GABA-gated bacterial homologue, we identified a novel site in α5 $GABA_A$ receptor subunits. **Conclusion and Implications:** Our findings support previous studies suggesting a link between some of the therapeutic effects of clozapine and its negative modulatory action on certain $GABA_A$ receptor subtypes. The novel site we describe in this study is a new potential target for optimizing antipsychotic medications with beneficial polypharmacology.

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