Tricyclic antipsychotics and antidepressants can inhibit α5-containing $GABA_A$ receptors by two distinct mechanisms

Konstantina Bampali[1], Filip Koniuszewski[1], Luca Silva[1], Sabah Rehman[1], Florian Vogel[1], Thomas Seidel[2], Petra Scholze[1], Florian Zirpel[1], Arthur Garon[2], Thierry Langer[2], Matthäus Willeit[1], and Margot Ernst[1]

[1]Medical University of Vienna
[2]University of Vienna

January 12, 2022

Abstract

Background and Purpose: Many psychotherapeutic drugs, including clozapine, display polypharmacology and act on $GABA_A$ receptors. Patients with schizophrenia show alterations in function, structure and molecular composition of the hippocampus, and a recent study demonstrated aberrant levels of hippocampal a5 subunit-containing $GABA_A$ receptors. The purpose of this study is to investigate tricyclic compounds in a5 subunit-containing receptor subtypes.

Experimental Approach: Functional studies of effects by seven 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 a5 subunit, probing a novel binding site. Radioligand displacement data complemented the functional and mutational findings.

Key Results: We show that the antipsychotic drugs clozapine and chlorpromazine exert functional inhibition on multiple $GABA_A$ receptor subtypes, including a5-containing ones. Based on a chlorpromazine binding site observed in a GABA-gated bacterial homologue, we identified a novel site in a5 $GABA_A$ receptor subunits and demonstrate differential usage of this and the orthosteric sites by these ligands.

Conclusion and Implications: Despite high molecular and functional similarities among the tested ligands, they reduce GABA currents by differential usage of allosteric and orthosteric sites. The C C C C C C site we describe here is a new potential target for optimizing antipsychotic medications with beneficial polypharmacology. Further studies in defined subtypes are needed to substantiate mechanistic links between the therapeutic effects of clozapine and its action on certain $GABA_A$ receptor subtypes.

Hosted file

`Bampali et al_MS_revised.pdf` available at https://authorea.com/users/406835/articles/517350-tricyclic-antipsychotics-and-antidepressants-can-inhibit-%CE%B15-containing-gabaa-receptors-by-two-distinct-mechanisms