



Review

Mechanism of action of clozapine in the context of dopamine D₁-D₂ receptor hetero-dimerization – a working hypothesis

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Abstract:

The tight correlation between the clinical potency and the D₂R blocking action of antipsychotic medications suggests that dopamine hyperactivity plays a significant role in psychosis. Clozapine, one of the most effective antipsychotic drugs, has been shown to display moderate affinity for various neurotransmitter receptors, including the dopamine D₁ and D₂ receptors; however, the exact mechanism of action of clozapine has not yet been fully elucidated. Here, we describe our working hypothesis pointing to the role of dopamine D₁-D₂ receptor hetero-dimerization as a mechanism of action of clozapine. It has been widely assumed that D₁ and D₂ receptors are segregated to separate neuronal populations; however, other data suggest that D₁ and D₂ receptors are co-expressed by a moderate to substantial proportion of striatal neurons, as well as in the medial prefrontal cortex. Our recent studies indicate that concomitant stimulation of both D₁ and D₂ dopamine receptors induces an increase in their hetero-dimerization. In order to confirm the working hypothesis that clozapine influences D₁-D₂ receptor oligomerization, we employed fluorescence resonance energy transfer (FRET) technology, using fluorescently tagged dopamine receptors and fluorescence lifetime microscopy of intact living cells. The effect of clozapine on D₁R-D₂R hetero-oligomerization was strongly dependent on the drug concentration; the lower concentration, which resulted in binding to the high affinity sites, decreased the transfer efficiency, while the higher concentration of clozapine enhanced transfer efficiency. Further investigation confirmed the idea that high affinity binding sites exist when the receptor is coupled with G protein, and also that clozapine attenuates the hetero-oligomerization of a high affinity pool of dopamine D₁-D₂ receptors. The results discussed in the present study, showing the effect of clozapine on D₁-D₂ receptor hetero-oligomerization, together with the data pointing to the importance of receptors forming hetero-oligomers as a novel level for pharmacological intervention help to increase the understanding of the molecular mechanism of action of antipsychotic drugs.

Key words:

dopamine receptors, hetero-dimerization, FRET, clozapine, schizophrenia
