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

Marta Dziedzicka-Wasylewska1,2, Agata Faron-Górecka1, Andrzej Górecki2, Maciej Kuśmider1

1Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

2Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, Gronostajowa 7, PL 30-387 Kraków, Poland

Correspondence: Marta Dziedzicka-Wasylewska, e-mail: wasyl@if-pan.krakow.pl

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