Active-state model of a dopamine D_2 receptor - $G\alpha_i$ complex stabilized by aripiprazole-type partial agonists

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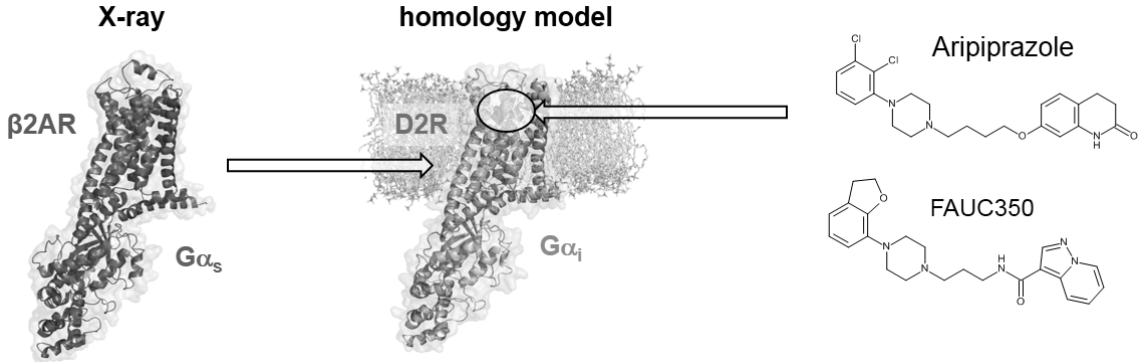
Partial agonists exhibit a submaximal capacity to enhance the coupling of one receptor to an intracellular binding partner. Partial agonism at dopamine D_2 receptors (D2R) has been suggested to exert beneficial effects on schizophrenia, a chronic mental illness characterized by hypo- and hyperfunctions in monoamine neurotransmitter systems including mesolimbic and mesocortical dopaminergic pathways [1]. Due to their stabilizing effect on monoamine pathways, especially the dopaminergic pathways, dopamine receptor partial agonists such as aripiprazole represent promising options for the treatment of schizophrenia [2,3].

To understand the structural determinants of partial agonism better, we performed molecular-dynamics simulations employing our recently described active-state homology models of the D2R-$G\alpha_i$ protein-complex [4] coupled to the partial agonists aripiprazole and a closely related compound, FAUC350, and compared the impact of these ligands on the conformation of the ternary complexes with those of previous simulations with the full agonist dopamine.

We found that the two partial agonists are capable of differently regulating the shape of structural motifs, including the extracellular loop regions, the binding pocket and, in particular, intracellular G protein-binding domains. As G protein-coupling to certain intracellular epitopes of the receptor is considered to be the key step of allosterically triggered nucleotide-exchange [5], it is tempting to assume that impaired receptor-G protein-coupling due to distinct ligand-specific conformations is a major determinant of partial agonist efficacy.



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