Structure of the D1 Dopamine Receptor and Binding of Ligands
Adam Griffith, Scott Oloff*, Nagarajan Vaidehi, William A. Goddard III

The family of dopamine receptors, which are Class A, Rhodopsin-like, G-protein coupled receptors (GPCRs), contains two subgroups based on homology to either the D1 receptor or the D2 receptor. The D1-like subgroup contains the D1 and D5 receptors which activate adenylyl cyclase, while the D2-like subgroup contains the D2, D3, and D4 receptors which inhibit adenylyl cyclase.

The D1 receptor (sometimes called D1A) is more widespread than the other dopamine receptors and tends to show up in greater density. It is present in the central nervous system where it is involved in movement, drug abuse (particularly cocaine), and memory and cognitive function. It has also been linked to Parkinson’s disease and schizophrenia. D1 is also present in the kidneys and is linked to hypertension. The high degree of sequence similarity between the dopamine receptors, in particular between D1 and D5, makes it difficult to develop subtype-selective ligands to further explore the possible uses of dopamine receptor modulation.

The structure of the D1 receptor was predicted using Membstruk. The transmembrane (TM) prediction procedure was modified slightly. Following the overall prediction, refinement of each TM region was performed using individual TM sequences to get results that are more specific to each TM region, rather than specific to the protein as a whole. This modified procedure is now becoming standard practice. The structure prediction procedure was also changed slightly. The rotational optimization of the helices was performed with lipid present, resulting in a better defined energy profile at the expense of added computation time.

A set of 20 ligands was docked to the predicted D1 structure using MSCDock. The antagonists are: LE300 (with 5 derivatives) and SCH23390 (with 6 derivatives, including SCH39166 and SCH24518). The agonists are: A77636, A68930, SKF38393, dihydrexidine (DHX), dinapsoline, dinoxylene, and dopamine. Docking showed that dopamine binds similarly in D1 and D2, but not identically. LE300 and two of its derivatives also showed binding sites similar to that of dopamine. The remaining ligands are still being examined.

Future work includes additional docking to the D1 structure as well as comparisons with the published D2 structure** and a predicted D5 structure.

* UNC, Chapel Hill