3D-model structure of the D2 dopamine receptor bound to the atypical antipsychotic drug risperidone

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Background

Risperidone is a widely prescribed atypical antipsychotic drug and inverse agonist for the D2 dopamine receptor. This drug, once bound, elicits the formation of a hydrophobic patch in the binding pocket of DRD2.[1] The presence of Risperidone causes the residue I184 (on extracellular loop 2) to undergo a small helical turn across the binding pocket to face residues Trp100 (on extracellular loop 1) and residue L94. These three residues interact to form the hydrophobic patch. This patch prevents other ligands from binding to the DRD2 receptor, and this leads to the inverse agonist nature of Risperidone.

Methodology

We utilized D2 dopamine receptor and risperidone constructs downloaded through the NIH 3D-printing website in order to accurately create our model.[2, 3] After uploading these constructs to TinkerCad software, we pinpointed the positions of the residues, constructed them, and created the shown model. To depict the receptor-ligand interactions, we screen-recorded manual movements of the model.

Model

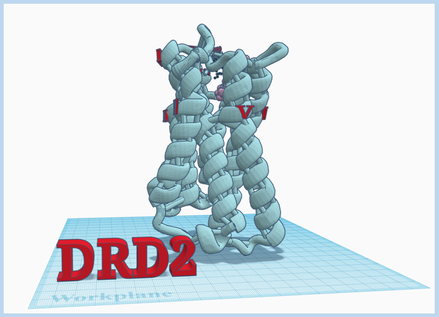


Fig. 1 Frontal View of DRD2

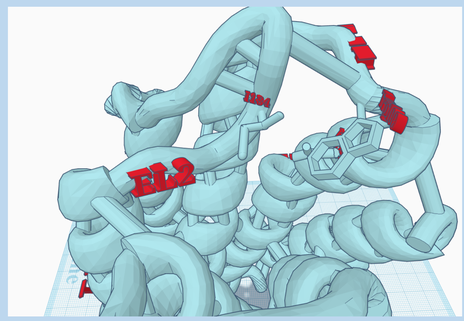


Fig. 2 Unbound DRD2 Receptor

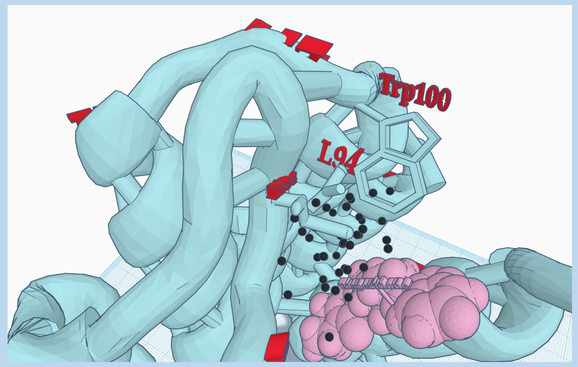
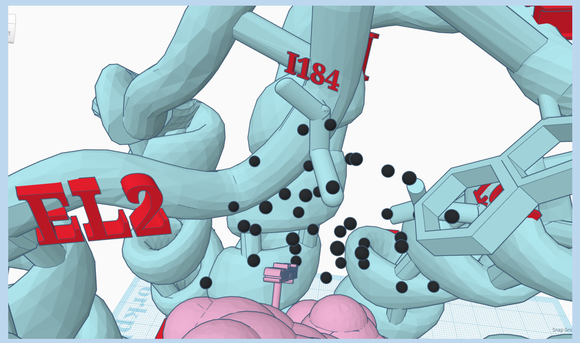


Fig. 3 Risperidone (pink) bound to binding pocket, and formation of Hydrophobic Patch (black matrix) created by residues (red)

Fig. 4 Risperidone (pink) bound, and formation of the hydrophobic patch (black matrix) after the turn of I184 (location under red label)



Our model effectively demonstrates the binding of Risperidone to DRD2 and its associated structural changes by offering a visual representation. While we had to make changes to the model following the inability to 3D print it due to COVID-19 closures, this final receptor model could be applied to future research regarding risperidone and the D2 dopamine receptor.

Discussion

We had originally planned to 3D print this ligand-receptor interaction, and physically represent movement through the use of magnets. Our digital model was necesary in lieu of constraints, but it provided more liberties for labeling as well as an easier visualization for movement. Using this model, we are able to depict the real-time formation of the hydrophobic patch as the binding of Risperidone encourages the movement of residue I184 towards L94 and Trp100.

Dysfunction of the dopaminergic system is implicated in diseases such as Schizophrenia, Parkinson's Disease, Major Depressive Disorder, and Attention-Deficit/Hyperactivity Disorder.[1] The DRD2 dopamine receptor is therefore a common target for pharmaceutical interventions, such as the use of atypical antipsychotics. The Risperidone-DRD2 model reveals structural changes that explain binding properties of Risperidone and could be used to explain properties of similar antipsychotics.

References

1. Wang, S., Che, T., Levit, A., Shoichet, B., Wacker, D., & Roth, B. (2018). Structure of the D2 Dopamine Receptor Bound to the Atypical Antipsychotic Drug Risperidone. *Nature News*, 269–273. doi: 10.2210/pdb6c38/pdb.
2. Dopamine Receptor Construct. (2017). Retrieved from https://3dprint.nih.gov/discover/3DPX-007449.
3. Wadhwani, K. (2018). Risperidone. Retrieved from https://3dprint.nih.gov/discover/3dpx-009767.