Molecular Basis of Pramipexole's Preferential Binding D3 over D2 Receptors

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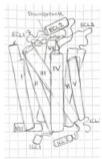
Background/Abstract

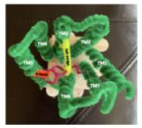
- Pramipexole is a dopamine agonist used to treat Parkinson's disease (PD) (Brooks, 2000).
- Biased toward D3 receptors
- D3 receptors are greatest in the substantia nigra, globus pallidus, and ventral striatum of the motor circuit (Foll et al, 2014).
- Modeling pramipexole-D3 binding allows for understanding of complex receptor-ligand interactions and the reason for D3 bias

Methods

- Research on pramipexole binding affinity as well as D2 and D3 receptor structure and receptor-drug interactions



- 2D sketches of D2 and D3 receptors, 3D prototyping and digital design.
- The models focus on the receptor-ligand interactions to highlight the basis of D3 bias.



- 3D prints of both receptor models with connectors that represent major receptor-drug interactions.

Future Directions

- Screen novel compounds for thiazole cores similar to pramipexole
- Novel compounds with thiazole cores may be better D3 agonists due to improved selectivity, affinity, or solubility.

Member Contributions

- Research on Molecular Interactions: GH, SKN
- Digital Design of Model: AB
- 3D Printing: SKN
- Teaching Guide: GH, SKN, NM
- Poster: GH, AB
- Spark Video: SKN, AB

Design Process

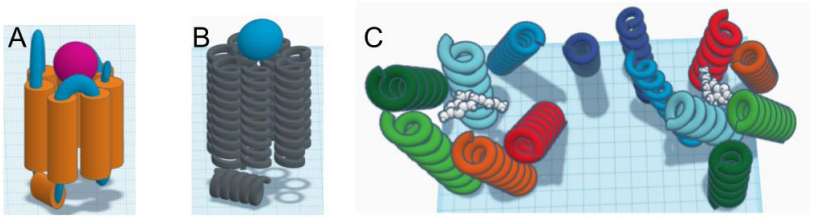


Figure 1. Early iteration stages of the 3D model. A & B. We focused on the general receptor structure, (7 TM domains) and the location of the binding pocket. C. We focused on examining the differences between the helices in D2 vs D3 and used a more accurate model of pramipexole.

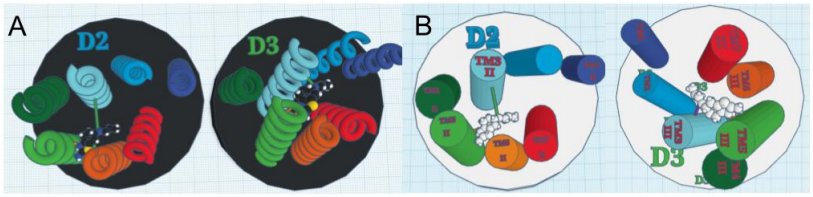


Figure 2. 3D Model of the ligand binding. A. We focused on bonding differences between TM domains and ligand. Modeled bonds through different colors and lengths. B. Remodeled using cylinders instead of spirals for 3D printing.

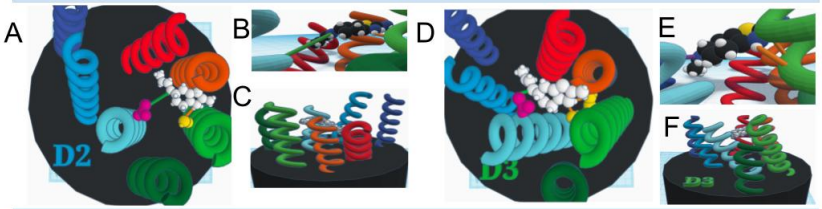


Figure 3. Most recent 3D digital model. We added specific amino acid side chains at points of pramipexole-TM domain interaction. Color coordinated transmembrane helices (dark blue: I, blue: II, teal: III, dark green: IV, lime green: V, orange: VI, and red: VII). A. D2 receptor; salt bridge (lime green) and hydrogen bonds (orange). B & C. Side views. D. D3 receptor. E & F. Side views

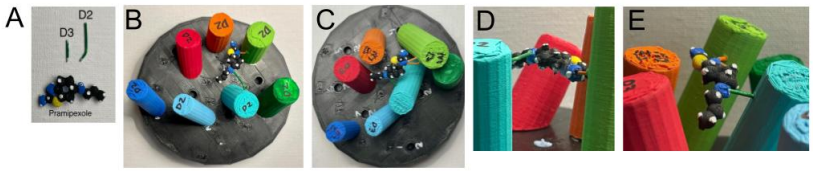


Figure 4. 3D Printed models. A. Pramipexole and modeled salt bridges to demonstrate the shorter salt bridge of the pramipexole-D3 interaction. B. 3D printed D2 receptor with green salt bridge and orange hydrogen bond. C. 3D printed D3 receptor with geen salt bridge and orange hydrogen bonds. D. Side view of D2 (TMIV removed). E. Side view of D3 (TMI removed)

Teaching Guide

- 1st iteration: remove a lot of text, add more pictures and visuals → 2nd iteration: supplement the introductory lock-key model to bridge intro-level students → 3rd iteration: expand on more basic ideas and significantly simplify the teaching guide

Implications

- Molecular basis of pramipexole's bias → screening mechanism for other PD drugs with similar structures

Future Directions

- Future directions: model proposed pharmaceutical agents with thiazol cores to infer their binding affinities → examine the modeled interaction of proposed drugs with D2 and D3
- Future iterations of the model: include pi overlap of D3 and thiazol of pramipexole, as well as hydrophobic interactions. Model conformational change that occurs when ligand binds.

Receptor	Involved TM	Involved Residue(s)	Bond Type
D2	III, IV, V	- Asp114, Val190, and Ser194	H-bond (1), salt bridge (1), (Platania et al, 2012)
D3	III, V, VI	- Ser192, Ser193, Hist349, Asp110	H-bond (2), salt bridge (1), π overlap (Chen et al, 2008)

References

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