a2A Adrenoreceptor Interaction with Norepinephrine

Scan our teaching guide for a walk through of the binding process using our 3D printed models!

Ali Alvarez, Emma Fritsch, Nancy Chen, Sandy Sundar Rajan

Background

- The a2A adrenoreceptor is a subtype of adrenoreceptors
  - Targets norepinephrine activity in our CNS and PNS
  - Primarily exist in vascular presynaptic nerve terminals
  - It is a high target for drug design to treat the effects of stimulation
  - Stimulation causes hypotension, sedation, analgesia[2]

- Binding of norepinephrine to these receptors inhibits the release of norepinephrine
  - Believed to play a role in depressive disorder & schizophrenia

- The a2A adrenoreceptor is a G protein receptor
  - Made up of 7 trans membrane alpha helices
  - Coupled with a Gi or Go protein
  - There is difficulty establishing models of GPCR due to the criteria of being membrane bound
  - Current experiments use homology & molecular modelling[1]

Significance & Purpose

Our Goal: To create a 3D model of the crystallized alpha-2A adrenoreceptor & demonstrate the binding of norephinephrine from a digital model[1]

This particular adrenergic receptor plays a role in drug therapies targeting high blood pressure, muscle spasms, and ADHD.
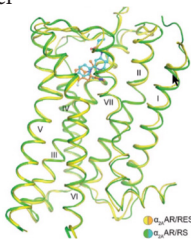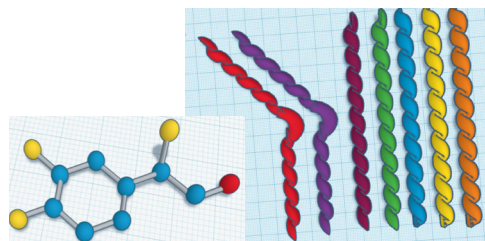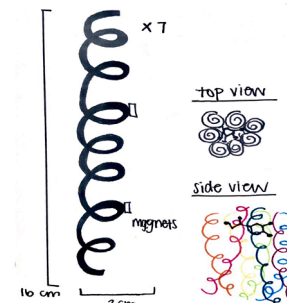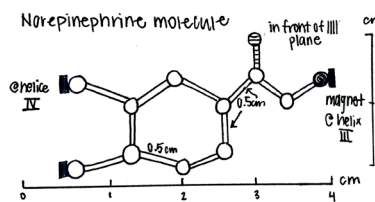

Troubleshooting

- Initial issues with sizing in TinkerCad - the components were too large for 3D printing and were scaled down by 50%
- Faced issues with printing standing receptor - decided to lay each helices flat
- The additional 4 helices were interupted during 3D printing
- A clay form was needed in order to stand up the 3D model

Design Process

Design Iterations

(1) Built a preliminary model using pipe cleaners, hot glue, and clay from the UNC MakerKit
(2) Created design sketches using Ostopovici-Halip computer generated model for scaling
(3) Used TinkerCad to develop a first draft of our receptor & a NE molecule
(4) Printed first draft using Ultimaker 3D printers & CPE material at UNC's Be A Makerspace - 3D printer & 101 BeAM training was completed prior to printing (painted with acrylic paint to mirror the TinkerCad computer model)
(4) With hot glue & magnets, we assembled the 7 subunits & fit the receptor into binding pocket for our final product

Discussion & Implications

This 3D representation will help elucidate the specific binding region on the receptor and allow for improvements in drug design.
  - Aids in exploring the configuration of a receptor that can only be seen microscopically
  - Allows for comprehension of receptor structure for introductory NSCI students
  - We can see the overall binding area of the NE molecule
  - We identified the residues that NE is targeting through hydrogen bonding at helices III and V

Future Directions:
In the future, we hope to be able to model a more specific receptor that focuses in on the residues that are involved in the binding affinity of the norepinephrine molecule.

References

(1) Ostopovici-Halip, L., Curpan, R., Mracec, M., & Bologa, C. G. (2011). Structural determinants of the alpha2 adrenoceptor subtype selectivity. Journal of molecular graphics & modelling, 29(8), 1030–1038.
(2) Zhao, Suwen (2019). Structural Basis of the Diversity of Adrenergic Receptors. Cell Reports, 29, 2929-2935.e4.
(3) Maletic, V., Eramo, A., Gwin, K., & Offord, S. J. (2017). The Role of Norepinephrine & Its Adrenergic Receptors in the Pathophysiology & Treatment of Major Depressive Disorder & Schizophrenia. Frontiers in psychiatry.
(4) Halip, L. Curpan, R. Lukinich-Gruia, Mircea, A. (2008). 3D Homology: alpha2A. Adrenergic Receptor Subtype. Revue Roumaine de Chimie. 54.
(5) Norepinephrine. ChemSpider. *Chemical Structure & Function*. Retrieved February 28, 2021.