SMART Teams 2013-2014 Research and Design Phase

Brookfield Academy Upper School SMART Team

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Modeling the Alcohol Binding Site of the NMDA Receptor Using the GluA2-receptor Structure

PDB: 3KG2

Primary Citation: Sobolevsky, A.I., Rosconi, M.P., Gouaux, E. (2009) AMPA subtype ionotropic glutamate receptor in complex with competitive antagonist ZK 200775. *Nature* 462**:** 745-756.

Format: Alpha carbon backbone

RP: Zcorp with plaster

Description:
With 2.96 gallons of ethanol consumed per capita, Wisconsin has one of the highest rates of alcohol abuse in the United States. According to the National Institute of Alcohol Abuse and Alcoholism, approximately 744,330 people are regularly blocking their N-Methyl-ᴅ-aspartate Receptor (NMDA) receptors with alcohol, inhibiting cognition, short-term memory formation, motor coordination, and overall central nervous system (CNS) function. The Brookfield Academy SMART (Students Modeling A Research Topic) Team used 3D printing technology to model the alcohol binding site on the NMDA receptor. The NMDA receptor is an ion channel in the membrane of neurons in the brain that is activated by the neurotransmitter glutamate. Upon binding, glutamate opens the ion channel, allowing the passage of calcium and sodium ions, which excite the cell and control multiple intracellular signaling pathways. In the presence of alcohol, this essential ion gate is often shut, inhibiting the flow of ions and therefore leading to the well-known symptoms of intoxication. The NMDA receptor is composed of 4 subunits: 2 GluN1 and 2 GluN2A, the latter of which has multiple subtypes (A-D), GluN2A being the most common. Alcohol is believed to bind to the transmembrane domain of the receptor at four sites. These binding sites comprise the amino acids Gly638, Phe639, Phe639, Leu819, and Met818 (of subunit GluN1) and Met 823, Phe636, Leu824 and Phe637 (on GluN2A). By mutating the amino acid sequence in each NMDA subunit, Dr. Peoples and his team are able to directly manipulate alcohol sensitivity. Interestingly enough, mutations in the same position on different subunits can drastically modulate the inhibition of the receptor by alcohol. Further understanding of NMDA receptor mechanisms could lead to better treatments for long-term alcohol abuse.
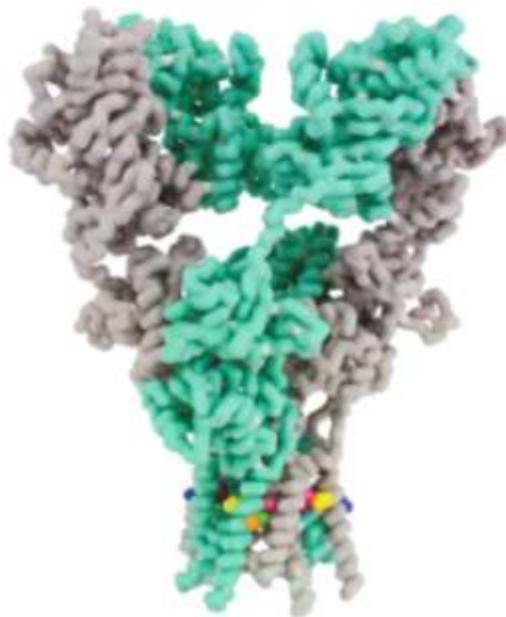
Specific Model Information:

**The NMDA model was built using the crystal structure for the rat GluA2 receptor. Amino acid and structural alignments were used to determine the respective positions of the NMDA amino acids within the GluA2 protein. The program, DeepView / SwissPDB-Viewer (website: http://spdbv.vital-it.ch/) was used to substitute the appropriate amino acid side chain into the GluA2 structure file.

- GluN1 – (Chain A and Chain C) are colored silver.
- Amino acid side chains involved in the alcohol binding site displayed in spacefill.
  - Glycine638 is colored red.
  - Phenylalanine639 is colored magenta.
  - Methionine818 is colored yellow.
  - Leucine819 is colored lime.
  - Valine820 is colored medium blue.
  - GluN2 – (Chain B and Chain D) are colored turquoise.
- Amino acid side chains involved in the alcohol binding site displayed in spacefill.
  - Phenylalanine636 is colored magenta.
  - Phenylalanine637 is colored magenta.
  - Methionine823 is colored yellow.
  - Leucine824 is colored lime.
  - Alanine826 is colored orange.
- Structural supports are colored white.

Corresponding Amino acid side chains between NMDA and GluA2 protein structures

GluN1	GluA2
G638	G607
F639	G608
M818	M798
L819	L799
V820	V800
GluN2	**GluA2**
F636	F607
F637	F608
M823	M798
L824	L799
A825	A800

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