Alcoholism and the NMDA Receptor

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Abstract:

Alcohol affects our world more than any other drug. As the third leading preventable cause of death, it is adolescents' drug of choice, and parental alcoholism impacts the lives of one in four children. Alcohol consumption interferes with communication between neurons in the central nervous system, causing effects such as motor incoordination and memory impairment. The NMDA (N-Methyl-D-aspartate) receptor, an ion channel located within neuronal membranes, is a major target upon which alcohol acts. When activated by the signaling molecule glutamate, a gate in its membrane-associated (M) domains opens, allowing calcium and sodium cations to enter the neuron through its ion channel. Alcohol, however, interferes with this process by binding to the M domains, preventing cations from entering the neuron and causing many of the known effects of alcohol consumption. Mutations at positions in the M domains, such as M823 in the GluN2A M4 domain and F636 in the GluN2A M3 domain, have been found to significantly alter alcohol sensitivity; making it less susceptible. The Kettle Moraine High School SMART (Students Modeling A Research Topic) Team has modeled the NMDA receptor using 3D printing technology to investigate structure-function relationships. Further research on the interactions between alcohol and the NMDA receptor could aid in finding a solution to the abuse of this historically documented and often detrimental drug.

Alcoholism: A Modern Plague

Alcohol is the third leading cause of preventable death in the United States. It affects people of all ages, from babies with fetal alcohol syndrome, to adolescents who binge drink, to alcohol-impaired drivers who cause car accidents. Alcohol can claim lives and tear families apart. Approximately 17 million adults were reported to have an alcohol problem in America in 2012. Physiologically, alcohol alters the balance of neurotransmitters in the brain. Alcoholics and heavy drinkers feel compelled to drink- it is a physical dependency that does not allow them to have 'just one'. Unable to quit, they are unable to live their lives without the inhibitory effects of alcohol.

The new research on the NMDA receptor could lead to new ways to help alcoholics recover. With the research being done, better treatments and detox programs could be devised to take a stand against this devastating illness.

The NMDA Receptor: A Major Target of Alcohol Action

Mutations at positions in the M domains of the receptor, such as M823 in the GluN2A M4 domain and F636 in the GluN2A M3 domain, have been found to significantly alter alcohol sensitivity; making it less susceptible to inhibition. Several more amino acid sites that have been identified to play a role in alcohol sensitivity have also been highlighted on the receptor model. NMDA receptors are important in learning and memory, judgment, and coordination- thus the inhibition of the NMDA receptor by alcohol can have harmful psychological effects. Evidence observed in experimental test subjects (both animal and human) indicate that NMDA receptor antagonists produce effects very similar to those of alcohol; however these blockers can also decrease alcohol cravings in humans. Though previously performed studies had focused on the GluN2A subunit of the NMDA receptor, recent research points to a greater importance in the role for the GluN2B subunit in interactions with alcohol molecules. Dr. Peoples' laboratory has recently found an amino acid in the M3 domain of the GluN2B subunit, F637, that can regulate alcohol sensitivity. Further research on the interactions between alcohol and the NMDA receptor could aid in finding a solution or more effective intervention for treatment of alcoholism.

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NMDA Receptor Structure and Model Information:

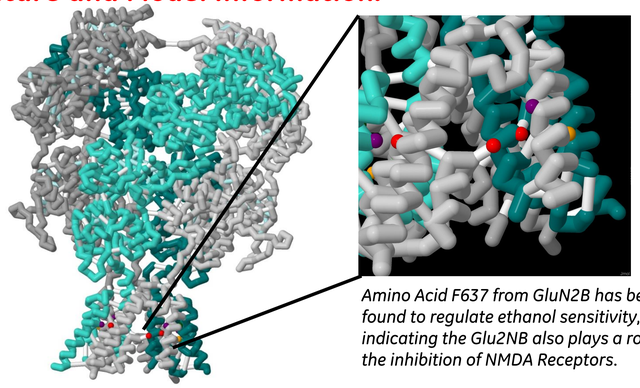
Heterotetrameric:
GluN1A -Light Grey
GluN1B - Dark Grey
GluN2A - Turquoise
GluN2B – Teal

H bonds - Pale Turquoise
Struts – Silver

PDB: 4PE5

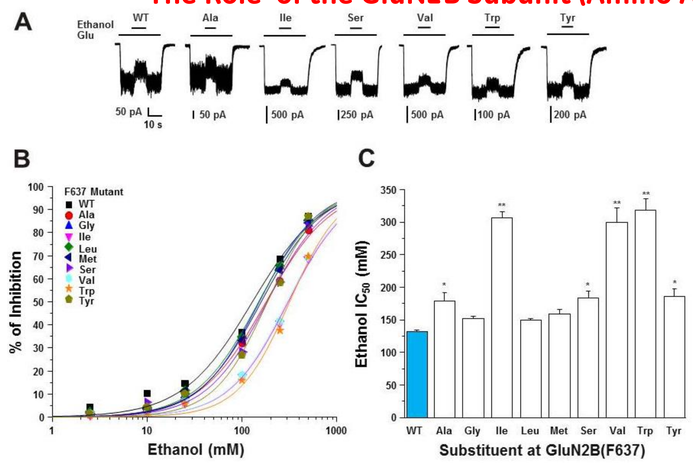
Highlighted amino acids have been found to play a role in ethanol sensitivity.

Highlighted Amino Acids:
Gly638 - Blue
Phe639 - Red
Leu819 - Purple
Val820 - Light Green
Ala821 - Orange
Phe637 – Red
Phe638 - Red
Met824 - Dark Green
Leu825 - Purple
Gly826 – Blue



Amino Acid F637 from GluN2B has been found to regulate ethanol sensitivity, indicating the Glu2NB also plays a role in the inhibition of NMDA Receptors.

The Role of the GluN2B Subunit (Amino Acid F637) in Ethanol Sensitivity:



WT indicates wild-type for all three figures.

FIGURE A: shows traces of currents from NMDA receptor patches with various substitution mutations at site GluN2B(F637). The receptor was activated by 10 μM glutamate with 50 μM glycine and 100 mM of ethanol was applied for inhibition.

FIGURE B: shows the concentration-response curves for ethanol inhibition of the NMDA receptors for various substitution mutations at site GluN2B(F637).

FIGURE C: shows the concentration of ethanol at which glutamate-activated current by the NMDA receptors is reduced by half for various substitution mutations. Mutations that cause significant differences from wild-type are marked with an asterisk.

Methods of Data Collection: Whole-cell patch clamp recording was used to study the activity of the NMDA receptor when the cell was exposed to glutamate and ethanol. A glass electrode with a flattened microscopic tip is placed into contact with the cell membrane, resulting in a very high resistance electrical seal between the cell membrane and the microelectrode tip. After the membrane under the tip is ruptured, the electrode can record changes in electrical potential caused by ion channels in the cell when glutamate and ethanol are added. The effects of ethanol on the NMDA receptor's response to glutamate is recorded by measuring the amplitude of the electrical currents carried through the ion channels.

Conclusion:

As demonstrated by figures A, B, and C, further research into the role of subunit GluN2B in inhibition may better explain how alcohol acts in the M domains to block NMDA receptor gating. Further investigation into the NMDA receptor from the studies of researchers such as Dr. Peoples will only help build the molecular understanding of alcohol's effects on the brain and body; and may eventually lead to more effective medical interventions to advance the treatment of alcoholism that is so prevalent in today's society. Although much more research needs to be done before any such drugs or treatments are determined, the research presented today is working towards specifying which areas and amino acid sites in the NMDA receptor protein merit a closer look.

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"Alcohol Facts and Statistics." *National Institute on Alcohol Abuse and Alcoholism*. NIAAA, July 2014. Web. 11 Feb. 2015.