Alcohol, or ethanol, is one of the most abused drugs worldwide, dating back to ancient cultures including Mesopotamia. Effects of alcohol on behavior are well-known, such as incoherence and lack of coordination. Overconsumption of ethanol can lead to alcoholism, which is related to genetic variations and brain chemistry.

In the brain, proteins such as the N-methyl-D-aspartate (NMDA) receptor are responsible for multiple cognitive functions. The NMDA receptor binds glutamate, a major neurotransmitter, transferring signals from one neuron to another across the synapse, or gap between neurons. When ethanol is not present in the system, glutamate binds to the NMDA receptor on the postsynaptic cell and opens the ion channel, allowing sodium and calcium to enter and excite the cell. Ethanol, when present, crosses the protective blood-brain barrier and appears to bind to specific amino acid side chains: Ala825, Phe637, Met823, Val820, Phe639, and Leu824, which are in the transmembrane portion of the NMDA receptor GluN1 and GluN2A subunits. Ethanol limits NMDA receptor function by inhibiting the ion channel gate from opening and depolarizing the membrane. When ethanol binds to sites in the transmembrane domain, the conformational change of the NMDA receptor is inhibited, blocking the flow of sodium and calcium into the neuron, preventing synaptic transmission. By learning how ethanol interacts with the NMDA receptor to change its function, researchers hope to discover better treatments for alcoholism. The Cudahy SMART Team (Students Modeling A Research Topic) modeled the NMDA receptor, highlighting important structures, using 3D printing technology.

Abstract

Alcohol, or ethanol, is one of the most abused drugs worldwide, dating back to ancient cultures including Mesopotamia. Effects of alcohol on behavior are well-known, such as incoherence and lack of coordination. Overconsumption of ethanol can lead to alcoholism, which is related to genetic variations and brain chemistry.

In the brain, proteins such as the N-methyl-D-aspartate (NMDA) receptor are responsible for multiple cognitive functions. The NMDA receptor binds glutamate, a major neurotransmitter, transferring signals from one neuron to another across the synapse, or gap between neurons. When ethanol is not present in the system, glutamate binds to the NMDA receptor on the postsynaptic cell and opens the ion channel, allowing sodium and calcium to enter and excite the cell. Ethanol, when present, crosses the protective blood-brain barrier and appears to bind to specific amino acid side chains: Ala825, Phe637, Met823, Val820, Phe639, and Leu824, which are in the transmembrane portion of the NMDA receptor GluN1 and GluN2A subunits. Ethanol limits NMDA receptor function by inhibiting the ion channel gate from opening and depolarizing the membrane. When ethanol binds to sites in the transmembrane domain, the conformational change of the NMDA receptor is inhibited, blocking the flow of sodium and calcium into the neuron, preventing synaptic transmission. By learning how ethanol interacts with the NMDA receptor to change its function, researchers hope to discover better treatments for alcoholism. The Cudahy SMART Team (Students Modeling A Research Topic) modeled the NMDA receptor, highlighting important structures, using 3D printing technology.

The Process of Synaptic Transmission

Nerves communicate by sending chemical signals, called neurotransmitters, across the space between cells, called a synapse. To accomplish this, a neurotransmitter is released from a vesicle in a presynaptic neuron, the neuron initiating the signal process. The neurotransmitters are released into the synapse and bind to receptor proteins on the postsynaptic neuron, continuing transmission of the signal, called an action potential. When an excitatory neurotransmitter binds to a receptor protein, such as the N-methyl-D-aspartate, NMDA, receptor, it causes a conformational change to the protein, allowing sodium to enter the postsynaptic neuron from the intercellular space. When sodium enters the postsynaptic cell, the cell voltage becomes more positive, depolarizing it to reach threshold. This is the necessary voltage for an action potential to occur in the postsynaptic neuron. If the neurotransmitter is inhibitory, it will oppose depolarization to threshold.

NMDA Receptor Under Normal Conditions

Neuronal signaling requires the release of a neurotransmitter into the synaptic cleft. In the absence of alcohol, an excitatory neurotransmitter, glutamate, is released by the presynaptic neuron. Upon binding to the NMDA receptor on the postsynaptic neuron, which is a sodium channel, glutamate stimulates the influx of sodium ions through the channel and into the postsynaptic neuron, depolarizing it. As shown in the figure below, if this excitatory postsynaptic potential (EPSP; a voltage change) reaches threshold, the minimum voltage change needed to stimulate an action potential, the neuronal signal continues through the system.

NMDA Receptor When Ethanol is Present

When ethanol, or alcohol, is present in the synapse, it can attenuate the propagation of the neuronal signal. Ethanol binds to the transmembrane portion of the NMDA receptor at specific amino acid residues at four potential binding sites in the M3 and M4 domains. These interactions are likely the result of hydrophobic interactions between ethanol and the receptor. When bound to the receptor, ethanol prevents the ion channel from fully opening. As shown in the figure below, the EPSP does not reach the threshold needed to induce an action potential. When this happens in the brain, functions such as judgment, coordination, and planning are impaired.

Data Supports the Role of Specific Amino Acid Residues in the NMDA Receptor as the Sites Influenced by Alcohol

Ethanol reduces the Na⁺-produced current across the NMDA

• Amino acids in key positions were mutated and current across the receptor was measured and compared to wild-type in response to the addition of glutamate alone, and glutamate in the presence of ethanol.

• Sodium-producing currents are shown in the graphs to the left. An elevated line indicates inhibition.

• Data reveal that when mutated in key positions, ethanol did not inhibit the sodium current as effectively as in the wild-type, thus indicating the importance of these amino acids in binding ethanol.

Higher concentrations of ethanol required in mutations to elicit inhibition

• Different mutations required different concentrations of ethanol for inhibition, with the F636 mutant being the least sensitive to the effects of ethanol.

• Data show Ala825, Phe637, Met823, Val820, Phe639, and Leu824 are the key residues to bind ethanol.

Ethanol Sensitivity and Brain Function

Alcohol primarily affects the frontal lobes of the brain. When alcohol, or ethanol, blocks the N-methyl-D-aspartate receptor the person experiences loss of motor coordination and inhibitions. Alterations in sensitivity of brain target proteins may be why alcoholics drink more. They may be less sensitive to ethanol, so it takes more ethanol to achieve the same effect as someone who is more sensitive.

Conclusions

The effects of alcohol on the human body are outwardly visible. Many areas in the brain are affected by alcohol, including inhibition of judgment or reason. This is partly achieved through the block of the NMDA receptor by ethanol. Through research on the NMDA receptor, one can see the effects of ethanol at the molecular level and perhaps a potential link to alcohol sensitivity can be determined through an understanding of which amino acids interact directly with ethanol. From these studies an effective treatment of alcohol abuse and alcoholism may be discovered.