The Alcoholism Problem in America

Alcohol abuse in the United States, specifically in Wisconsin, is a huge problem. According to the United States Centers for Disease Control and Prevention, each year 88,000 people die from alcohol-related causes in the United States. Ethanol misuse, a deadly and expensive societal problem, cost the United States $249 billion in 2010.1 According to the 2014 National Survey on Drug Use and Health (NSDUH), 13.8% of people ages 12-20 were binge drinkers.2 In Wisconsin alone, the prevalence of binge drinking is 24.4%, which is the second highest in the nation.3 This can lead to alcohol abuse later in life, and only 35.9% of people ever recover.4 If researchers can develop pharmaceuticals to help minimize the effect of ethanol on the brain, it could reduce the cost of alcoholism to society.

Synapses Are Affected by Alcohol

Learning and memory, cognition, and motor function are all controlled by electrical impulses in the brain. An electrical impulse travels from neuron to neuron through junctions called synapses (see figure 1). A chemical transmitter is stored in vesicles in the presynaptic neuron terminal which, when released into the synaptic cleft, stimulates receptors on the post-synaptic neuron. When the post-synaptic receptor is stimulated to a threshold, an electrical impulse is sent along the second neuron. The end result is transmission of information. When this transmission is strengthened, it results in learning and memory in the brain.

Ethanol (figure 2) can bring this learning and memory to a screeching halt. Specifically, the ethanol molecule targets the N-Methyl-D-Aspartate receptor (NMDAR). Ethanol affects the NMDAR by making it harder for the ion channel to open and stay open. When the ion channel isn’t open, the post synaptic neuron can’t be stimulated, and the impulse is halted. This will impair learning and memory, cognition, and motor function.

The N-Methyl-D-Aspartate Receptor

The N-Methyl-D-Aspartate receptor (NMDAR) is a type of glutamate receptor-ion channel found in the brain’s neurons. It mediates much of the excitatory synaptic transmission for learning and memory, cognition, and motor function. Normally, the NMDAR is activated when glutamate binds to it, allowing positive ions to flow through the cell membrane (see figure 3). However, alcohol, when present in the body, inhibits the NMDA receptor. The NMDAR has four major regions: the amino terminal domain, the ligand binding domain, the membrane-associated (M) domains, and the carboxy terminal domain (see figure 4). The NMDAR is a heterotetrameric protein with two GluN1 and two GluN2 subunits.

Ethanol interacts with the NMDAR in the M domains mainly at four residues in GluN1 and four in GluN2B (see figure 5).6,7 Glutamate interacts with the NMDAR in the ligand binding domain.

Ethanol Closes the NMDAR

The current response of a neuron to glutamate is inhibited when ethanol interacts with the NMDA receptor (see figure 6).10 These measurements were recorded using the patch-clamp technique (see figure 7).

When ethanol interacts with the NMDAR, it binds to certain amino acids. In order to find which amino acids those are, each amino acid is replaced with tryptophan. This allows researchers to see if the mutant receptor keeps working in the presence of ethanol (see figure 8).

Why Study the NMDA Receptor?

By determining the locations of ethanol interactions on the NMDAR, researchers may be able to alter the protein to the point where these interactions no longer take place; therefore, the brain would not be inhibited by ethanol. If further research can develop drug molecules to help minimize the effect of ethanol on the brain, it could reduce the cost of alcoholism to society.

References