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Alcohol alters prefrontal cortex activity through ion channel disruption

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Researchers have long believed that abnormal function in the prefrontal cortex (PFC) region of the brain contributes to the impulsive behavior and lack of control over drinking that characterize alcohol dependence, but how this occurred was unknown. This study used rodents to examine the effects of alcohol on three specific ion channels that control the activity of PFC neurons, finding that N-methyl-D-aspartic acid (NMDA) receptors are especially sensitive to alcohol disruption.

“The prefrontal cortex is a part of the brain that helps us decide whether we should take actions or not,” said John J. Woodward, a professor in the department of neurosciences and the Center for Drug and Alcohol Programs at the Medical University of South Carolina. “It weighs the relative risks and benefits of our behavior and normally protects us from risky or dangerous actions or those that may be inappropriate during social situations. When the PFC is damaged or its activity is decreased, behavior can change dramatically and people can lose much of their inhibition and ability to weigh the consequences of their actions.”

Woodward, also the corresponding author for the study, explained that ion channels are gates in the neuron membrane that let ions into and out of the cells when appropriate. “We reasoned that alcohol may affect one or more of these ion channel gates, leading to alterations in the function of the prefrontal cortex … and that this may contribute to an individual’s inability to control their drinking,” he said. “This may help to explain why many alcoholics appear to lose control over their drinking despite serious adverse consequences that can arise, such as loss of job, family

or even health."

Researchers used general anesthesia to humanely euthanize male Sprague-Dawley rats. Their brains were quickly removed, chilled, sliced, and placed in a chamber for recording electrical activity. Using sophisticated single-cell neuron recording techniques, the researchers measured currents carried by NMDA, gamma-aminobutyric acid (GABA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the absence and presence of alcohol.

"Our major finding was that alcohol, at concentrations that are associated with mild to moderate intoxication – blood alcohol levels of 0.08 percent and above – significantly inhibited the function of the NMDA receptor ion channel without affecting AMPA or GABA ion channels," said Woodward.

"Our results provide an explanation for how alcohol affects the ability of the prefrontal cortex to carry out its normal duties," he said. "When NMDA receptors are inhibited, as with alcohol, the ability of the neuron to carry out its task is affected, thereby reducing the ability of an individual to control their behavior and possibly leading them to engage in actions that are not beneficial. In other words, the normal risk/benefit assessment that this brain region engages in is disrupted."

"While potent alcohol effects on NMDA receptors (NMDAR) and NMDAR-mediated transmission have been seen in past studies in other brain regions," added David Lovinger, chief of the Laboratory for Integrative Neuroscience at the National Institute on Alcohol Abuse and Alcoholism, "what stands out about this paper is that this effect is seen in the absence of alterations in other aspects of transmission. This selectivity is more pronounced than what has been seen in brain areas such as the hippocampus, amygdala and cerebellum."

Lovinger said that targeting this receptor with pharmacological agents might be an effective strategy for treating problems of alcohol abuse and alcoholism, particularly if future research could identify the specific subtype of NMDAR affected by alcohol. “It would also be helpful to determine if the alcohol effects on NMDA receptors contribute to neuroadaptations or neurotoxicity in this brain region after prolonged ethanol exposure, thereby contributing to alcoholism and alcoholic brain damage.”

“These types of studies are important because they show that alcohol has specific effects on ion channels that control the activity of neurons,” observed Woodward. “This means that it is possible to determine how alcohol causes its effects on the brain, to understand how these changes lead to uncontrolled drinking and, eventually, to develop better treatments for alcoholism.”

Source: National Institute on Alcohol Abuse and Alcoholism