A brain protein called vimentin can indicate damage to the hippocampus following binge drinking

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Chronic drinking is known to have detrimental health effects such as cardiac and liver problems, cognitive impairments, and brain damage. Binge drinking in particular is known to increase the risk of developing dementia and/or brain damage, yet little is known about an exact threshold for the damaging effects of alcohol. A study using rodents to examine various markers of neurodegeneration has found that brain damage can occur with as little as 24 hours of binge-like alcohol exposure.

Results will be published in the March 2013 issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"We know that the extent of damage following alcohol exposure depends heavily on the manner in which it is consumed," said Kimberly Nixon, associate professor of pharmaceutical sciences at The University of Kentucky as well as corresponding author for the study. "Human studies suggest that binge-pattern drinking is more closely associated with brain damage. One study, for example, reported that binge drinking at least once per month in adulthood significantly increases the risk of developing dementia later in life. Animal models help provide the critical information that binge drinking, which produces high blood alcohol levels, directly causes damage."

"The exact threshold for the damaging effects of alcohol on the brain is

unclear," commented Fulton T. Crews, John Andrews Distinguished Professor and director of the Center for Alcohol Studies at the University of North Carolina. "It is likely that the higher the blood alcohol level the greater the damage, however, this manuscript only studies binge drinking, using vimentin and flurojade B as markers of neurotoxicity."

"People hear from multiple sources that low-moderate alcohol consumption can be beneficial, and then we come along and say that heavy alcohol use leads to detrimental outcomes," said Nixon. "People then want to know what the line is between beneficial and detrimental Unfortunately, we don't know exactly. However, our study suggests that it may be even less than previously thought."

Nixon and her colleagues administered a nutritionally complete liquid diet to adult male Sprague-Dawley rats that additionally contained either alcohol (25% w/v) or isocaloric dextrose every eight hours for either one or two days. The rodents were sacrificed immediately following, two days after, or seven days after alcohol exposure and their brain tissues were examined.

"This was really a simple study that took advantage of some new 'tools' to look for evidence of brain damage," explained Nixon. "In other words, we didn't look for dying cells themselves, but we looked at more indirect indices of damage by looking at what happens to astroglia, one of the 'supporting' cells for neurons. Astroglia react to brain damage by expressing several proteins that they do not normally express under healthy, happy conditions, one of which is an intermediate filament protein called vimentin. We saw a remarkable number of cells expressing this marker It is one of those 'here is your brain, here is your brain on drugs' kind of findings where the expression was obvious to the naked eye in many brains with as little as 24 hours of high blood alcohol levels."

Nixon added that, because rodents metabolize alcohol significantly faster than humans do, it is important to look at the actual concentration of alcohol in the blood in order to translate this to the human condition. "These rats had blood alcohol levels that were more than four times the legal driving limit, which for humans would require excessive drinking in the nature of a 12-pack of beer, a couple bottles of wine, or half of fifth of whisky. Unfortunately, drinking self-reports and blood alcohol level data from emergency rooms confirm that this level of drinking is common in those with alcohol use disorders."

"Rodent brain damage can model human damage," noted Crews. "Vimentin seems to be a good marker of glial activation that shows that one day of binge drinking can cause some brain damage that persists and grows after a week of abstinence. However, both rodent and human brain damage generally require long-term alcohol consumption that models alcoholism and not the acute responses studied in this manuscript."

Nixon agreed. "The lack of overt neuronal deterioration suggests that a single, short-term, high-level binge probably does not result in functional changes and/or cognitive deficits," she said. "However, since alcoholics experience multiple binges throughout their lifetime, it is important to consider that each successive binge, starting with the very first one, affords some level of damage to the brain. Therefore, theoretically, with multiple binges comes a cumulative detrimental effect where pronounced cognitive, behavioral, and structural effects are observed."

Nixon said this study demonstrates that new discoveries are always possible. "You have to know where and when to look for some of these effects," she said. "The reason why this discovery wasn't made previously is merely due to groups, ourselves included, not taking the time to thoroughly investigate these lower threshold doses with some pretty specific time points. Chasing down a threshold is not a sexy topic

and it was actually fairly risky in that it was possible that we would have had all negative effects. Nonetheless, the take-home message of our data is that even one short-duration binge-alcohol experience – which is unfortunately similar to what young adults may experience during spring break or weekend partying - may start a cascade that leads to brain damage."

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