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Mouse Study Finds Alcohol-Damaged Livers Send Inflammatory Signals to the Brain in Alzheimer’s Disease

Researchers traced microRNA-122 in liver vesicles to brain tissue only in Alzheimer’s-model mice after repeated alcohol exposure

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Researchers at Beth Israel Deaconess Medical Center reported Friday, November 13, that repeated alcohol exposure in a mouse model of Alzheimer’s disease appeared to damage the liver in ways that may intensify inflammation in the brain, pointing to a possible biological link between alcohol-related liver injury and neurological disease.

The study, published in the Proceedings of the National Academy of Sciences, was conducted in mice and in laboratory-grown immune cells, not in people. The authors said the findings identify a possible mechanism of liver-to-brain signaling, but they do not show that alcohol causes Alzheimer’s disease in humans or measure the effects of moderate drinking.

The work focused on inflammation, which is already known to play a role in both Alzheimer’s disease and heavy alcohol use. Alcohol can also injure the liver, and liver disease has long been associated with changes in brain function. What has been less clear is how those processes may interact.

According to the researchers, mice engineered to model Alzheimer's disease responded to repeated alcohol exposure differently from healthy control mice. In the Alzheimer's model, alcohol caused liver damage that was not seen in the healthy animals. Inflammation also worsened in both the liver and the brain, suggesting that the presence of underlying disease made the animals more vulnerable to alcohol-related injury.

The team measured liver enzymes, fat metabolism, inflammatory signals and molecular traffic between the liver and the brain. Across more than two dozen measures, the Alzheimer's model diverged from the healthy controls. The biggest difference, the researchers said, involved tiny membrane-bound particles called extracellular vesicles, which are released by cells and carry proteins and genetic material to other parts of the body.

After alcohol exposure, liver cells released more of these vesicles than usual. The vesicles also carried higher amounts of microRNA-122, a regulatory molecule linked to normal liver function and commonly used by clinicians as a marker of liver injury. The researchers said microRNA-122 is typically not found in the brain.

In the study, alcohol caused the liver to pack more microRNA-122 into extracellular vesicles in both the Alzheimer's-model mice and the healthy controls. But only in the Alzheimer's-model mice did the molecule later appear in brain tissue. The researchers said they confirmed that the molecule had not been produced in the brain itself, which suggests it had traveled there from the liver.

Gyongyi Szabo, the study's senior author and chief academic officer at Beth Israel Deaconess Medical Center and Beth Israel Lahey Health, said in a statement that communication between the liver and brain has been described before, but the underlying mechanisms remain poorly understood. She said a better understanding of that signaling could point to new treatment targets in Alzheimer's disease, alcohol use disorder and metabolic conditions.

To test what the liver-derived material might do once it reached the brain, the researchers turned to microglia, the brain's resident immune cells. In laboratory experiments, the microglia absorbed the liver vesicles easily. The vesicles alone had

little effect. But when those same cells were later exposed to an inflammatory trigger, they reacted much more strongly than microglia that had not taken up the vesicles.

The researchers then tested microRNA-122 directly, delivering it into microglia without the surrounding vesicle and without exposing the cells to alcohol as part of that experiment. The cells still showed an exaggerated inflammatory response, although the effect was smaller than with the full vesicle. That result suggests other material carried inside the vesicles may also contribute to the immune reaction. When the team blocked microRNA-122, the heightened response largely disappeared.

The authors said the same pattern was seen when they used vesicles taken from the blood of patients with alcohol-associated hepatitis, a severe form of alcohol-related liver inflammation. Those vesicles also appeared to prime microglia for a stronger inflammatory response, adding a human tissue component to findings that otherwise came from mouse and cell models.

The study stops well short of showing what happens in patients with Alzheimer’s disease who drink alcohol. It also does not compare beer, wine or spirits, and it does not address whether low or moderate consumption carries the same biological effect seen under repeated alcohol exposure in this preclinical work. Even so, the findings add mechanistic evidence to a broader health issue that matters to the beverage industry and to consumers: alcohol’s effects may extend beyond the liver and involve signaling pathways that could affect the brain under some disease conditions.

That distinction is important because the study was designed to examine a mechanism, not to estimate real-world risk in the general population. The mouse model represented an Alzheimer’s-like disease state, and the strongest effects were seen in that setting. Healthy control mice did not show the same appearance of microRNA-122 in the brain.

The researchers said one unanswered question is why the Alzheimer’s-model liver behaved so differently from the healthy liver in the first place. Szabo said future studies using primary liver cells could help determine whether the Alzheimer’s genotype directly changes the release of extracellular vesicles.

The work was funded by the National Institutes of Health and the National Institute on Alcohol Abuse and Alcoholism. Beth Israel Deaconess Medical Center said Szabo has served as a paid scientific consultant to several biotechnology and pharmaceutical companies, holds stock options in two of them, and receives royalties from Springer Nature Group and UpToDate. The other authors reported no conflicts of interest.