Females more prone to brain damage from alcohol abuse

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Alcoholism has traditionally been considered a male disease because there are many more alcoholic males than females.

But a new study by researchers at Oregon Health & Science University and the Portland Veterans Affairs Medical Center suggests that women are more prone to brain damage from alcohol abuse than men.

The study led by Kristine Wiren, Ph.D., associate professor of behavioral neuroscience and medicine, OHSU School of Medicine, and research biologist, PVAMC Research Service, found that female mice are more susceptible to neurotoxic effects of alcohol withdrawal, including significantly increased brain cell death, than male mice. It also found the gender difference exists whether the animals are prone to severe withdrawal due to a genetic predisposition, or resistant to it.

Wiren said she was surprised by the results.

"We designed the experiment to be able to identify gene expression differences between lines of mice that are genetically selected for severe alcohol withdrawal compared with mice that are resistant to alcohol withdrawal," Wiren said. "I thought there would be a difference between the genders, but I didn't think it would be the most important thing."

She added, "The withdrawal severity phenotypes do show some differences, but they're subtle."

The study appears in the online edition of the journal *Neuropsychopharmacology*.

Wiren and Joel Hashimoto, research associate of behavioral neuroscience at OHSU and the PVAMC Research Service, examined four groups of selectively bred mice: two female groups, including one prone to severe withdrawal and one resistant to severe withdrawal, and two similar male groups. Four control groups also were used.

Using DNA microarray or "gene chip" analysis, a laboratory process involving advanced robotics that allows large numbers of genes and their complex interactions to be observed, Wiren and Hashimoto examined 5,000 genes from the prefrontal cortex, the area of the brain implicated in complex planning, personality expression and social behavior, and is involved in withdrawal-related brain circuitry. They then identified a total of 295 alcohol-regulated genes for each mouse group.

"We're interested in that part of the brain because it's important in inhibitory control. Alcoholics are unable to display good inhibitory control," Wiren said.

After identifying the alcohol-regulated gene pathways, Wiren and Hashimoto were able to home in on the extent of cell death. Ten days after alcohol withdrawal, they examined cells in the lateral parietal cortex area, which is part of the network of brain regions, in addition to the prefrontal cortex, involved in inhibitory control, and identified live and dead cells with tissue stains.

"At this one time point, which is the peak for cell death, we clearly see females are showing enhanced brain damage compared to the males. So, if you're female, the cells are dying; if you're a male, the cells are not," Wiren said. "We don't know the behavioral consequences of that, though."

What's more, Wiren and Hashimoto discovered, male brains respond to alcohol withdrawal much differently, in a potentially reparative manner.

"What we found in males is that almost 50 percent of the (alcohol-regulated) genes are involved in the pathway for cleaning things up," Wiren said. The genes respond with "removal of damaged proteins. The females have all this apoptosis (cell death) going on, and the males instead may have repair going on."

Such brain damage may underlie debilitating cognitive dysfunction and motor deficits observed in some alcoholics, according to the study. In addition, disruption of inhibitory functions in the prefrontal cortex may contribute to excessive drinking and the self-sustaining nature of alcoholism.

"The results suggest that females are more vulnerable to neurotoxic consequences of alcohol withdrawal," Wiren noted. "Everyone should be concerned about chronic alcohol consumption and severe intoxication, but females may be more vulnerable." This data is "consistent with some controversial human studies that suggest that females do develop more brain damage than male alcoholics."

Future studies, including one funded by the VA, will examine the role that hormones play in response to alcohol withdrawal, include the possibility that the male hormone androgen exacerbates cell death in males.

"What we're looking at now is the involvement of testosterone in mediating the cell death in females," Wiren said. "Not just in chronic conditions, but in acute (alcohol consumption) situations, testosterone levels drop in males. In females, they may rise."

Wiren also wants to look at a longer withdrawal time course. "Maybe

males show damage at a different time point," she said. "Or it might have happened earlier and they're showing repair."

Source: Oregon Health & Science University