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Cells show influence in alcohol sensitivity Genetic research on mice and flies may help humans

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Some people can drink a lot more alcohol than others without getting drunk. Now, after studying mice and fruit flies, scientists are starting to understand why.

Today in the journal Cell, two teams of researchers report that they have found surprising evidence that suggests that some of the genes that control the shape of nerve cells also help determine sensitivity to alcohol.

Taking into account earlier studies suggesting that reduced alcohol sensitivity increases susceptibility to drinking problems, scientists hope to decipher the basic biology underlying alcohol's effects in order to expose some of the biological roots of alcoholism.

Dr. Marc Schuckit, a professor of psychiatry at UC San Diego and a veteran investigator of alcoholism, said the findings present some "intriguing leads that open some new lines of research," noting that the alcohol-resistant animals, such as humans, tend to drink more when given the chance.

"If you get a gene variation that is impacting the intensity of the response to alcohol, and the amount of alcohol an animal drinks, of course I am going to look at that in humans," said Schuckit, who was not involved in the latest experiments.

In one line of experiments, a team at UCSF led by neuroscientist Adrian Rothenfluh and senior investigator Ulrike Heberlein of UCSF's Ernest Gallo Clinic and Research Center in Emeryville gave alcohol to fruit flies.

The studies showed that flies with a particular gene mutation

were remarkably resistant to alcohol doses that knocked normal flies flat on their backs. The resistant flies lacked a key regulatory protein, one of three proteins encoded by a gene that helps reshape brain cells during learning and memory formation.

Brain cells have a fluid structure, or "cytoskeleton," one mechanism in what neuroscientists call the brain's "plasticity." In effect, the tiny ends of the neurons sprout extra branches, strengthening the connections between nerve cells. Under the influence of alcohol, the normal flies showed more of this neuronal remodeling than did the resistant flies.

Separately, another research team, led by Pier Paolo Di Fiore at the Fondazione Istituto FIRC di Oncologia Molecolare in Milan, Italy, looked at a similar process in mice.

Some of the mice were bred without a gene shown to influence nerve-cell remodeling. Tests showed those mice were less intoxicated than normal mice when given a set amount of alcohol -- taking less time, for instance, to get back on their paws when turned on their backs.

Previous studies of alcohol's effects in the brain focused on receptors lining the surface of cells. The new work appears to be the first to highlight the importance of the cell's basic architecture, which could be influencing the actions of many receptors on the surface.

The mouse gene is known as Eps8, while in the fly it's called RhoGAP18B. Both are thought to have counterparts in people, although the precise human forms have yet to be identified.

Scientists said they have every reason to suspect the same systems are operating in people with alcohol-resistant metabolisms.

"This is a whole new kind of gene family implicated in the alcohol response," UCSF's Rothenfluh said, showing there is "clearly a link between addiction and neuronal plasticity."

It may even be possible someday to tweak the system, perhaps with a drug designed to alter the effects of alcohol in such a way as to reduce the alcoholism risk. But that's considered a longshot possibility, given the many unknowns and clear danger of toying with a process fundamental to brain function.

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