Medical Xpress

Researchers finds mechanism affecting alcohol consumption

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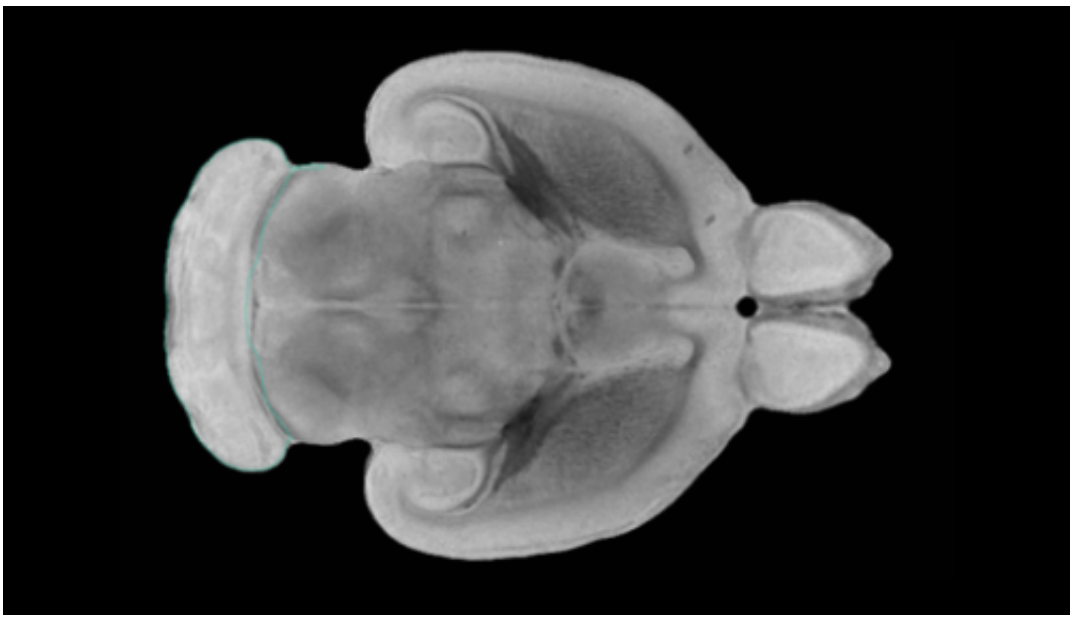

Cerebellum of CIVM postnatal rat brain atlas. Credit: Neurolex

A Washington State University researcher has found a mechanism that strongly influences whether or not an animal is likely to drink a lot of alcohol.

"It takes them from drinking the equivalent of three to four units of alcohol in one to two hours, down to one to two," said David Rossi, a WSU assistant professor of neuroscience.

Writing in the latest *Journal of Neuroscience*, Rossi and colleagues at the Oregon Health and Science University and the U.S. Veterans Administration Portland Health Care System said the mechanism offers a new target for drug therapies that can curb excessive drinking. It may be particularly effective among problem drinkers, half of whom are believed to have a genetically determined tendency to abuse alcohol.

The mechanism is found in the cerebellum, a part of the brain at the back of vertebrate skulls, in small neurons called granule cells. Sitting on the cells are proteins called GABAA receptors (pronounced "GABA A") that act like traffic cops for electrical signals in the nervous system.

When activated, the GABAA receptor suppresses the firing of neurons, or brain circuits. Benzodiazepines, which enhance GABAA signaling, reduce this excitability, which is why they are used to treat epilepsy.

Alcohol can also enhance GABAA receptor signaling and reduce firing in the brain, which is why it reduces anxiety and social inhibitions. In the cerebellum, it can lead to swaying, stumbling and slurred speech.

"You're inhibiting the circuit that executes normal motor function," said Rossi.

But alcohol does not act the same on every brain. In 2013, shortly before Rossi came to WSU from Oregon Health and Science University, he and his colleagues there linked the genes that influence ethanol consumption and the response of granule cell GABAA receptors to ethanol.

Much of their story is a tale of two specially bred mice.

The D2 mouse is a cheap drunk. After the equivalent of one or two drinks, it has trouble staying on a rotating cylinder.

"He won't drink much," said Rossi. "At most he'll have one or two drinks."

The B6 mouse, however, will stay on a rotating cylinder even after drinking three times as much alcohol, "which is beyond the drunk driving limit," said Rossi.

What's more, the D2 mouse is a teetotaler. After those first drinks, it stops. Under the right circumstances, the B6 mouse will binge.

"It mirrors the human situation," said Rossi. "If you're sensitive to the motor-impairing effects of alcohol, you don't tend to drink much. If you're not sensitive, you drink more."

In their earlier work, which was published in the journal *Nature Neuroscience*, Rossi and his colleagues saw clear differences in the way the cerebellar granule cell GABAA receptors reacted to alcohol in the two breeds of mice. In contrast to the D2 mouse, the cerebellar GABA receptors in the B6 mouse were suppressed by alcohol. Rossi called this "an obvious neural signature to a behavioral predilection to alcohol."

For the recent paper, Rossi and his colleagues injected a drug called THIP into the cerebellum of B6 mice. THIP activates the GABAA receptor, recreating the effect that alcohol has on low drinking D2 mice. It ended up deterring the B6 mice from drinking.

The finding, said Rossi, highlights a new region and new targets that can be manipulated "to deter excessive alcohol consumption, and potentially with fewer side effects than other existing targets and brain circuits."

More information: *Journal of Neuroscience*, DOI: 10.1523/JNEUROSCI.0042-16.2016

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