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Blocking boozy memories reduces risk of relapse

Molecule associated with learning and memory could be key to treating alcoholism.

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If former addicts could forget some of their sensory associations with a past of abuse, they might learn to avoid the cravings that can lead to a relapse.

Wiping out drinking-associated memories could help those with alcohol problems to stay sober, suggests a study in rats.

As with other forms of addiction, environmental cues linked to drinking — such as the smell of beer — can trigger the urge to consume alcohol and increase the risk of a relapse into abuse. Over time, these learned associations can be maddeningly difficult to break.

Scientists have now identified a potential molecular target in the brains of rats that could one day lead to treatments to help people stay dry. Dorit Ron, a neuroscientist at the University of California, San Francisco (UCSF), and her team show that strategically blocking the mTORC1 signalling pathway reduces alcoholic relapse by disrupting memories linked to past drinking. This pathway controls the production of several proteins associated with learning and memory.

A memory is thought to become vulnerable when it is retrieved, like a folder checked out from a library archive[1]. Pages can be shuffled or lost before the folder is returned to long-term storage. A number of studies have suggested that disrupting the mTORC1 pathway during this time window can destabilize the process of memory restoration and can potentially help treat post-traumatic stress disorder as well as drug addiction[2, 3].

In the latest study, published today in *Nature Neuroscience*[4], rats became problem drinkers after spending seven weeks exposed to a choice of water or a mixture of water and 20% alcohol. Ron says that the concoction probably tastes terrible to the rodents, but the animals eventually drink it in large quantities.

“It’s pretty amazing. You don’t do anything,” she says. “Over time, you can see they develop a strong preference for alcohol.” When the animals binged on alcohol, they reached concentrations of about 80 milligrams per 100 millilitres of blood — the legal driving limit in both the United Kingdom and the United States.

The researchers took alcohol away from the animals for 10 days and then gave each of them a tiny drop — just enough for the taste

and odour to reawaken alcohol-related memories. Immediately afterwards, some rats received a drug called rapamycin, which inhibits mTORC1 activity.

All the rats had been trained to press a lever to receive alcohol, but those that received rapamycin after memory reactivation showed significantly less inclination to do so over a two-week period.

Doctoring memories

“We don’t know what the specific memory is that we’re messing with, but we know the cue that’s triggering it,” says co-author Patricia Janak, a UCSF neuroscientist. Ron says that the memory trace disrupted by rapamycin is probably that which links the smell and taste to the pleasurable effects of alcohol consumption.

“It’s really excellent,” says Charles O’Brien, director of the Center for Studies of Addiction at the University of Pennsylvania in Philadelphia, referring to the study. “Fundamentally, addiction is a memory, and [the authors] are going straight at what is actually going on in the brain.”

Rapamycin does not seem to affect memory formation, but instead disrupts the reconsolidation of existing memories into long-term storage after they have been reactivated. Preliminary tests suggest that the drug’s effects can be quite specific, and do not affect the animals’ consumption of other desirable substances such as sugar-water.

Although Ron says her group does not plan to pursue studies in humans, she says that research by others may turn rapamycin or a related compound into an effective treatment for alcohol abuse. The US Food and Drug Administration has already approved rapamycin as an immunosuppressant for organ-transplant recipients.

“I would be eager to try this in my patients as soon as it can be determined that it’s safe,” says O’Brien.

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