

# Mechanism behind compulsive alcohol use

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Markus Heilig, professor of psychiatry at Linköping University. Credit: Anna Nilsen/Linköping University

A small group of nerve cells in the brain determines whether an individual continues to consume alcohol even when it has negative consequences. This is the conclusion of a study carried out on rats by researchers at Linköping University, Sweden. The scientists have

identified a previously unknown mechanism that may be a suitable target for treatment by medication. The study has been published in the scientific journal *Science Advances*.

"We discovered that a small group of nerve [cells](#) in a small region of the brain are the difference between being able to put the brakes on in a normal manner, as most of our rats did, and not being able to stop yourself," says Markus Heilig, professor of psychiatry in the Department of Biomedical and Clinical Sciences and director of the Center for Social and Affective Neuroscience (CSAN) at Linköping University. He has led the study on rats.

An important aspect of addiction is that only a minority of those who drink alcohol develop dependence. In other words—some people are more vulnerable than others. The researchers have investigated the mechanism behind one of the behaviors that characterize addiction, namely to continue using alcohol even though it brings [negative consequences](#), a behavior usually known as "compulsive use."

Making decisions, such as whether to take another drink or refrain, is complex. The brain has an important system for directed, motivated behavior. This system values things that we consider to be rewarding, such as tasty food, sex and also drugs, and drives us to seek more. But a brake is also needed, to prevent us from doing things that have adverse consequences. The brake balances information about possible negative consequences against the expected reward.

The first step in looking for molecular mechanisms behind compulsive alcohol use was to identify the vulnerable minority of individuals in whom these mechanisms may be in use. The rats in the study learned that they could press a lever to obtain a small amount of alcohol. After a period, the conditions changed, such that they received an electric shock together with the alcohol after pressing the lever. In this case, most rats

stopped pressing the lever for more alcohol. But the brake failed to function in around a third of the rats, and they continued to press the lever for self-administered alcohol even though it was now associated with discomfort.

In order to identify the group of nerve cells involved in compulsive alcohol use, the researchers used a marker that is formed in nerves just after they have been active. They found a network of nerve cells across several locations in the brain, where the hub of the network seemed to be in the central amygdala. The amygdala is a center in the brain that controls fear reactions and is involved in learning mechanisms that are coupled with fear. Three years ago, the research group published the results from a study into another behavior associated with alcohol addiction, namely choosing alcohol in preference to another reward. They showed that this behavior is also controlled by the central amygdala. The scientists could switch the behavior on and off by manipulating molecular mechanisms in this part of the brain.

In the study they have now published, the researchers identified a small group of nerve cells in the central amygdala, PKC $\delta$ -positive nerve cells, that promoted alcohol use in the vulnerable minority of rats, despite negative consequences. Around 4% of these cells constituted the network of cells that lay behind the failure of the brake for this specific behavior. When the researchers used advanced molecular methods to switch off these cells, the ability of the [rats](#) to refrain from self-administered alcohol was restored. It was the PKC $\delta$ , an enzyme, that proved to play the key role. The discovery raises hope that this enzyme is a possible target for new drug treatments.

"I had not expected that such a small group of [nerve](#) cells would be so decisive for this complex behavior. And I could not have imagined that it would be possible to demonstrate so clearly, by manipulating these cells from outside, that they cause the behavior," says Markus Heilig.

New results from other researchers suggest that also humans and other [animal species](#) can be divided into two groups with respect to their ability to brake reward-seeking behavior when it may have negative consequences. Markus Heilig believes that more research is needed to identify clinical markers that can reveal whether a person has an individual vulnerability for developing addiction. Early discovery may make it possible to use preventive measures.

"We must understand that the inability to brake behavior that is becoming detrimental is an important risk factor, and also maintains addiction once it has developed. We must reinforce the ability to [brake alcohol](#)-seeking activity in people who run an increased risk of developing addiction, not only by working with their behavior but also by developing medications that target the [molecular mechanisms](#) behind the behavior," says Markus Heilig.

**More information:** A neural substrate of compulsive alcohol use, *Science Advances* (2021). [DOI: 10.1126/sciadv.abg9045](https://doi.org/10.1126/sciadv.abg9045)

Provided by Linköping University

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