

Scientists are on trail of treatment for traumatic memories

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The dream of a drug that can help ameliorate the stress associated with durable traumatic memories, in order to treat disorders such as PTSD, has come a step closer to reality, according to a preclinical study led by

researchers at the Perelman School of Medicine at the University of Pennsylvania.

Published in the *Proceedings of the National Academy of Sciences*, the study identified an enzyme called ACSS2 (acetyl-CoA synthetase 2) as a regulator of the consolidation of long-term fear memories in rodents. Knocking out the ACSS2 gene, or administering a short-acting ACSS2 inhibitor compound, reduced mice and rats' ability to form long-term memories of fearful events.

"Our findings suggest that ACSS2 is an attractive target for the treatment of past traumatic memory conditions including PTSD," said study co-senior author Shelley L. Berger, Ph.D., the Daniel S. Och University Professor in the Department of Cell and Developmental Biology and director of the Epigenetics Institute at Penn.

Painful memories are a fact of life, but for some people, [traumatic events](#) embed themselves in memory so strongly that they cause chronic stress and anxiety, leading to mental illness. Thus, researchers in recent decades have begun to hunt for biological targets that, when blocked or enhanced, could weaken stress associated with traumatic memories or make them less durable—without harming overall memory or learning ability more generally. The new study was an initial demonstration, in experiments with rodents, that ACSS2 could be one such target.

ACSS2's job as an enzyme is to catalyze the production of acetyl-coenzyme A (acetyl-CoA), a small molecule that serves as a carrier in the cell of a key cofactor called an acetyl group. Among its many actions, acetyl-CoA uses its acetyl payload to carry out a process called histone acetylation, which controls [gene activity](#)—including the gene activity needed to turn new, temporary memories into long-term memories. Berger's lab has shown in prior research that ACSS2, through its role in histone acetylation, is particularly important for the formation

of long-term spatial memories in adult mice.

In the new study, the researchers investigated ACSS2's role in forming long-term fear memories in adult mice. Fear memories in this sense are memories of unpleasant incidents that alter mouse behavior.

The team first developed a line of mice in which the ACSS2 gene was disabled. They found that the absence of the gene did not impair ordinary, short-term working memory or other mouse activities, but did significantly reduce the strength of long-term memories, including fear memories. The researchers also confirmed a reduction, in these mice, of histone acetylation and gene activity changes normally associated with long-term memory consolidation. These findings provide strong support that ACSS2 is an ideal target for a [potential drug](#) to lower stress associated with trauma.

Next, the team injected normal mice and rats, immediately before and after fear-conditioning, with a compound that inhibits ACSS2 activity but is active for only a few hours. Compared to the rodents that were untreated, the treated ones showed significantly less fear behavior when exposed to stimulus 24 hours later—indicating that the process of long-term memory consolidation had been partly blocked when the ACSS2 inhibitor was active. Importantly, the effect of the inhibitor was specific to periods where new gene activity is required—drugs administered outside the consolidation window had no impact on the strength of memories formed.

Lastly, the scientists used a rat model of PTSD, in which rats are exposed to a predator scent (cat urine) and tested a week later for heightened signs of anxiety when exposed to the scent. Here again, the presence of the ACSS2 inhibitor during the memory-consolidation window reduced subsequent anxiety signs in the treated rats, compared to control rats.

The findings are preliminary; any ACSS2-blocking compound would require years of further testing, including extensive safety testing, before it could be approved by regulatory authorities and marketed as a drug. But in principle, such a drug could be used in the hours immediately after a traumatic event, to block or weaken the formation of an enduring stress memory of the event.

Indeed, such a drug might even be effective many days or even years after a traumatic event, in particular, during treatment of someone suffering from recurrent PTSD, such as in a psychological therapeutic setting.

"A process very similar to memory consolidation, called reconsolidation, occurs when we recall an event, and in principle, blocking that reconsolidation process by blocking the [histone acetylation](#) that supports it could therapeutically weaken even old [traumatic memories](#)," said study first author Desi Alexander, a Ph.D. candidate in Berger's lab.

The researchers are also hopeful that this approach could work in treating addictions, which, like post-traumatic stress, are learned behaviors embedded in [memory](#). "We look forward to developing this research further, including translating this treatment into a functional therapy," said Berger.

More information: Desi C. Alexander et al, Targeting acetyl-CoA metabolism attenuates the formation of fear memories through reduced activity-dependent histone acetylation, *Proceedings of the National Academy of Sciences* (2022). [DOI: 10.1073/pnas.2114758119](https://doi.org/10.1073/pnas.2114758119)

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