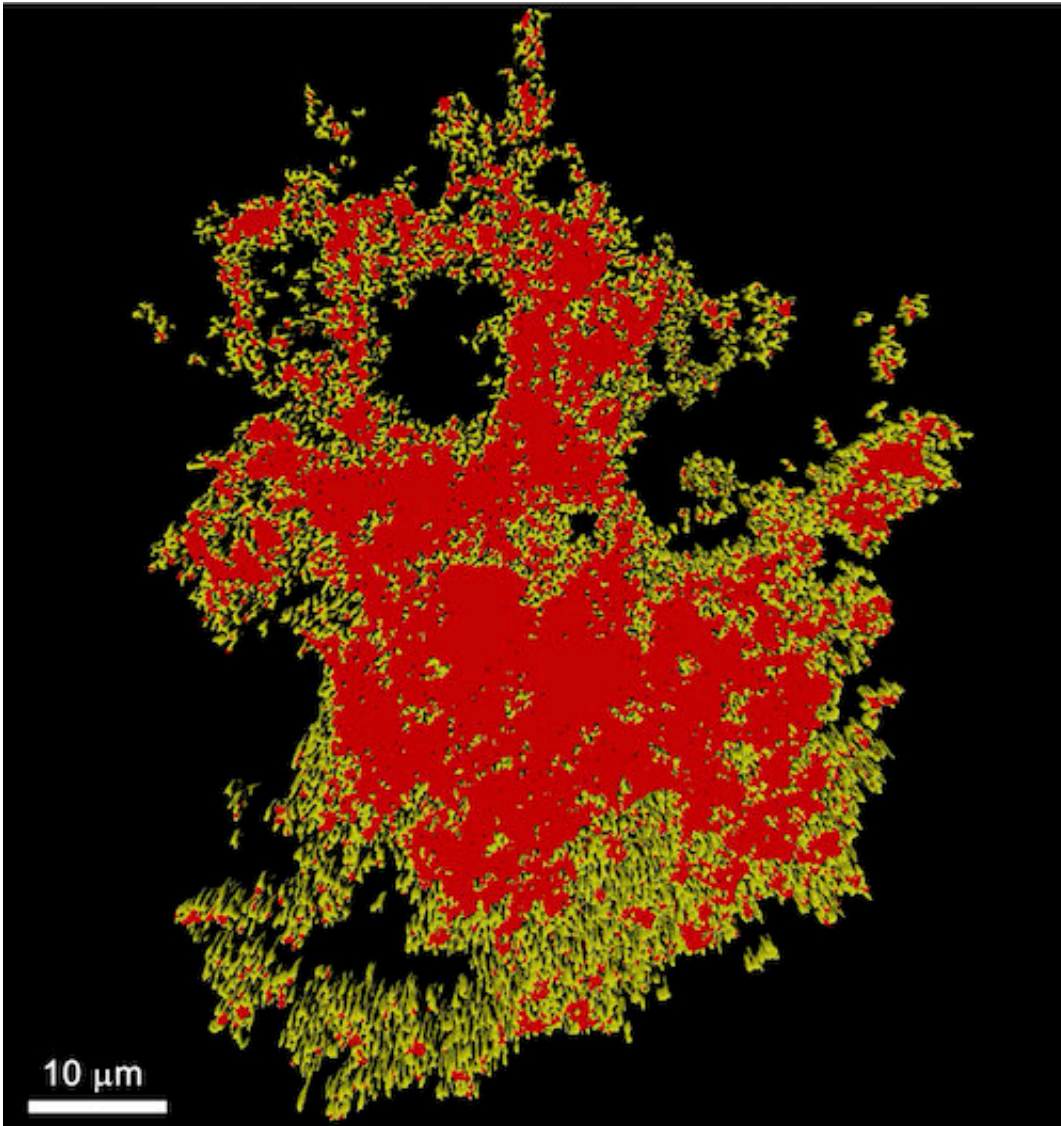


Putting the brakes on heroin relapse

October 5 2022, by Amy Ward, Sutton Scarboro and Kathryn Carter



A star-shaped cell known as an astrocyte. Credit: Anna Kruyer, Medical University of South Carolina

Neuroscientists from the Medical University of South Carolina (MUSC) report in *Science Advances* that star-shaped brain cells known as astrocytes can "turn off" neurons involved in relapse to heroin. Drug-related cues in the environment can intensify the drive to seek drugs, leading to relapse. In this article, a team led by Peter Kalivas, Ph.D., and Anna Kruyer, Ph.D., both of the Department of Neuroscience, examined how astrocytes interact with neurons and whether astrocytes play an important role in regulating the response to drug cues.

When we learn how to ride a bike or solve a math problem, the messenger [cells](#) in our brain, known as [neurons](#), create connections that enable them to communicate better so that we can more easily perform that same task the next time. The same happens when we learn to associate pleasure with [harmful substances](#), like drugs. Neurons send strong messages to each other, motivating us to seek them out again and again.

Communication between neurons is directed by a variety of cells, especially a group of star-shaped cells called [astrocytes](#). Astrocytes surround our neurons and act as [traffic lights](#), regulating the communication between cells, especially during addictive behaviors.

Another important player in addiction and relapse is the chemical messenger glutamate. Glutamate excites neurons and causes them to fire [electrical signals](#) to communicate with one another. The Kalivas Laboratory has been pivotal in establishing the importance of glutamate. Through decades of research, Kalivas has developed the "glutamate hypothesis of addiction," said Kruyer.

According to that hypothesis, too much glutamate can cause our neurons to fire constantly in response to drug-related environmental cues. That constant firing puts communication between cells into overdrive, encouraging drug-seeking behavior and relapse.

Kalivas and Kruyer found that astrocytes can slow down overactive communication.

"Astrocytes are like a brake in a car and you're pushing it to stop the glutamate signal," said Kruyer.

But how exactly do they do it?

To answer that question, the researchers used a well-established model of heroin relapse. In the model, rats first learn to self-administer heroin by pressing a lever. Following the lever press, they receive the drug along with light and sound cues, allowing the rats to associate the cues with the drug. Then, the cue and the drug are removed, mimicking withdrawal. Finally, animals are given access to the cue again, and their lever pressing is a measure of drug-seeking and relapse.

Using this approach, Kruyer and Kalivas found that astrocytes adapt in two ways to reduce drug seeking during withdrawal. One family of astrocytes moves closer to neurons and guides glutamate away from the synapse, reducing communication between neurons. Another family increases expression of the glutamate transporter GLT-1, which mops up excess glutamate. In both cases, astrocytes act as brakes on neuronal communication during withdrawal.

However, fewer astrocytes were available to perform this braking function during the relapse phase, and they were located farther from the neurons. Using a special chemical technology, Kruyer and Kalivas were able to turn astrocytes on and off to change behavior, showing that these star-shaped cells play an important role.

Essentially, when astrocytes surround neurons," Kruyer explained, "they sop up the glutamate and shut off that synapse," she said. "However, when they retract from neurons, it is like you lost the brake."

These findings could provide new insights into how to prevent relapse.

"Since astrocytes in the normal brain undergo two adaptations to suppress relapse, we think they may be a valuable cellular target for development of therapeutics to target relapse in [substance use disorder](#)," said Kruyer.

Previous clinical trials have shown that reducing glutamate alone is not enough to prevent relapse in humans. These findings suggest the possibility that a combination regimen that not only reduces [glutamate](#) levels but also accentuates the braking effect of astrocytes could be more successful and warrant further study.

"Historically, neurons have received all of the attention when it comes to behavioral pathologies," said Kruyer. "Our findings show that we need to take a more holistic view of the nervous system and consider that [cell types](#) other than neurons have the capacity to influence behavior and might hold the key to treatment of relapse."

To set the stage for new astrocyte-based therapies, the Kalivas Lab is trying to identify potential gene targets.

"Many genes express in astrocytes that are not expressed in other brain cells, including neurons," said Kalivas. "Understanding which of these genes are critical for astrocyte regulation of relapse gives us a handle on how to design drugs that will selectively increase the ability of astrocytes to inhibit [relapse](#). This is an arm of active research in our lab, and we have identified a few [astrocyte](#)-selective gene products that may serve as targets in treating [substance use disorders](#)."

More information: Anna Kruyer et al, Plasticity in astrocyte subpopulations regulates heroin relapse, *Science Advances* (2022). [DOI: 10.1126/sciadv.abo7044](https://doi.org/10.1126/sciadv.abo7044)

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