

# Stress flips cocaine relapse to 'on'; research switches it back to 'off'

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A pile of cocaine hydrochloride. Credit: DEA Drug Enforcement Agency, public domain

A heartbreaking phenomenon of addiction is that just a brief stressful episode can [trigger relapse](#). In a detailed new cocaine addiction study conducted in rat models, which closely parallel human addictive

behavior, scientists have identified what appears to be taking place in the mammalian brain to make that happen and uncovered the molecular biology that allows them to switch the stress-induced relapse back off.

The findings, published in the journal *eLife*, suggest a new way to develop medicines to combat [relapse](#), even a day or so after stress has occurred.

"That's so critical because you don't want to be taking medication all the time in anticipation of stress," said senior author Julie Kauer, a professor of molecular pharmacology, physiology and biotechnology at Brown University.

## How relapse persists

At the heart of the study are kappa opioid receptors ( $\kappa$ ORs) on the surface of key brain cells. The  $\kappa$ ORs are already seen as targets for anti-addiction medication development, but to make effective therapies, researchers must pinpoint specific interactions. In the new study, Kauer's team of scientists at Brown and the University of Wyoming made observations both in behaving rats and in rat brain tissue to focus on how stress appears to trigger these receptors to cause relapse, how that relapse remains sustained and how that effect can be disrupted.

The study focused on the ventral tegmental area (VTA), where the brain reinforces behaviors related to fulfilling basic needs. Sometimes those are healthy needs, like food, but they can also be cravings for drugs, alcohol or nicotine. Within the VTA, the reward for fulfilling needs is mediated by neurons that pump out the neurotransmitter dopamine. Those neurons are curbed, however, by the inhibitory neurotransmitter GABA, through connections to other neurons called synapses.

Neuroscientists have known that, as in people, stress induces relapse in

rats. One mechanism is the release of a protein called dynorphin that naturally activates  $\kappa$ ORs. The new study provides evidence that after brief acute stress, dynorphin triggers a long-lasting change in the conformation of the receptors, specifically on the GABA-releasing synapses that inhibit dopamine-releasing neurons in the VTA.

This specific change, the results suggest, serves to disrupt GABA's ability to hold back the dopamine neuron activity that may drive [cocaine](#)-seeking. Once the conformational change is made in the  $\kappa$ ORs, the researchers found, that relapse-promoting change stays in effect for days without any additional stress or any continued need for dynorphin.

That  $\kappa$ ORs continue to behave the same way for days even after just one brief stimulus is a new finding in neuroscience, the authors wrote in eLife: "Ours is the first demonstration of experience-induced changes in constitutive activity of these receptors."

## Reversing relapse

In a previous paper, the researchers showed that the chemical norBNI could end the relapse. In the new paper, they showed that they could reverse relapse with norBNI in the rats even a full day after stress.

Now they also know more about how that works. In a key experiment in the new study, they showed that norBNI activates a molecular pathway in the neurons called JNK (pronounced "junk") to restore the  $\kappa$ ORs to their normal conformation that does not exhibit sustained signaling. They also showed that merely blocking dynorphin from binding to  $\kappa$ ORs did not restore GABAergic neuron activity and would therefore not be a productive drug development strategy.

In another experiment, they showed that while relapse can be prevented by blocking dynorphin release before stress occurs, blocking dynorphin

release after stress occurs does no good. Dynorphin's unfortunate work is already done.

Given their evidence, what Kauer's team theorizes is that stress, via dynorphin, flips a switch on  $\kappa$ ORs that turns off normal GABA signaling at the relevant synapses for days. Using norBNI is like flipping another switch, via JNK, that rescues normal GABA signaling.

In human pharmacology, Kauer acknowledged, norBNI is not favored because its effects persist for weeks and could cause unwanted side effects, but that's why it's helpful to know that it exploits the JNK pathway to do its work.

"JNK is going to be an important future avenue to go down," Kauer said. "Maybe you could use something other than norBNI to drive JNK."

That, in turn, could someday provide people who have recovered from cocaine addiction with a medicine that prevents to the return of cravings because of [stress](#).

**More information:** *eLife*, [DOI: 10.7554/eLife.23785](https://doi.org/10.7554/eLife.23785)

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