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Cocaine withdrawal: Emotional 'brakes' stay on after cocaine wears off

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Washington State University researchers have found a cellular mechanism that contributes to the lack of motivation and negative emotions of a cocaine addict going through withdrawal. Their discovery, published in the latest *Proceedings of the National Academy of Sciences*, offers a deeper look into the cellular and behavioral implications of addiction.

Bradley Winters, lead author of the *PNAS* paper and a freshly minted WSU doctor of neuroscience, says he, his major advisor Yan Dong, and colleagues at WSU, the University of Pittsburgh and the European Neuroscience Institute focused on cells that produce a signaling molecule called cannabinoid receptor 1, or CB1. Its main function is regulating the communication between nerve cells related to the functions like memory, motor control, perception, mood and appetite. Those same functions are affected by THC, the cannabinoid in its namesake cannabis, or marijuana.

"These receptors are not here just to make marijuana fun," says Winters. "Their main function is changes in how nerve cells communicate with each other."

The researchers studied the CB1 cells by producing a line of mice in which the cells that make CB1 were labeled fluorescently. The researchers could then identify the cells and target them with glass pipettes 1/100th the width of a human hair and record electrical currents they use to communicate with other nerve cells.

The CB1 cells act like brakes, slowing down activity in a brain region called the nucleus accumbens, which governs emotion and motivation.

"Cocaine causes profound cellular changes in the nucleus accumbens, but no one has ever looked at this type of cell, and these cells are important because they help organize the output," says Winters.

The researchers found that cocaine increases the excitability of the CB1 cells, in effect stepping on the brakes of emotion and motivation. When an addict is high on cocaine, the brakes are struggling to slow things down. The problem is, they stay on even when the cocaine has worn off.

"As you do cocaine, it speeds everything up, pushing you to a highly rewarding emotional state," says Winters. "It is kind of like going down a steep hill so you have to start riding that brake really hard. But then after the cocaine wears off and the hill levels out, you're still riding that brake just as hard. Now you're going down a regular, low-grade hill but you're going 2 mph because your foot is still jammed on the brake."

The result is a drag on the emotions and motivation of an addict in withdrawal—a drag that could be linked to sluggish activation of the nucleus accumbens.

"That state is like, 'I feel terrible and I don't want to do anything,'" says Winters. "You have the high and the crashing low and this low that you feel is what brings you back to the drug because you want to feel better and the drug is the only thing you feel motivation for."

Provided by Washington State University

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