UC SANTA BARBARA

THE Current

March 5, 2014
Julie Cohen

Cocaine and the Pleasure Principle

On the other side of the cocaine high is the cocaine crash, and understanding how one follows the other can provide insight into the physiological effects of drug abuse. For decades, brain research has focused on the pleasurable effects of cocaine largely by studying the dopamine pathway. But this approach has left many questions unanswered.

So the Behavioral Pharmacology Laboratory (BPL) at UC Santa Barbara decided to take a different approach by examining the motivational systems that induce an animal to seek cocaine in the first place. Their findings appear in today's issue of The Journal of Neuroscience.

"We weren't looking at pleasure; we were looking at the animal's desire to seek that pleasure, which we believe is they key to understanding drug abuse," said Aaron Ettenberg, a professor in the Department of Psychological and Brain Sciences who established the BPL in 1982. The lab has been particularly active in the development and use of novel behavioral assays that provide a unique approach to the study of drug-behavior interactions.

The findings suggest that the same neural mechanism responsible for the negative effects of cocaine likely contribute to the animal's decision to ingest cocaine. "Just looking at the positive is looking at only half the picture; you have to understand the negative side as well," said Ettenberg.

“It’s not just the positive, rewarding effects of cocaine that drive this desire to seek the drug” he said. “It’s the net reward, which takes into account the negative consequences in addition to the positive. Together the two determine the net positive output that will lead to the motivated behavior.”

Ettenberg’s team chose to study norepinephrine (also called noradrenaline), because cocaine is known to act upon this primary neurotransmitter. The researchers chose two places in the brain — the bed nucleus of the stria terminalis (BNST) and the central nucleus of the amygdala (CeA) — because both have been implicated in the aversive effects of such emotional processes as fear conditioning and general anxiety. Norepinephrine is a major transmitter in these two brain systems and plays a part in regulating anxiety.

Lead author Jennifer Wenzel chose a unique way to reproduce the results of previous work she had done at UCSB, where she earned her Ph.D. in 2013. An earlier study used reversible lesions in the BNST and CeA to block the function in these two areas and then examined their effects in a unique animal model of cocaine self-administration.

For that study, the investigators trained rats to run down a custom-built 6-foot-long runway for a daily dose of cocaine. Each day they responded more quickly than the last, demonstrating an increasing motivation to get cocaine.

“Over several trials, however, rats developed an ambivalence about entering the goal box: they rapidly approached the goal but then turned and retreated back toward the start box,” Wenzel explained. “These retreats can happen several times before rats finally enter the goal box and receive an injection of cocaine.”

This retreat behavior became more and more prevalent as testing continued and reflects the animals’ learning that negative effects (the crash) follow the positive effects (euphoria) of cocaine. Blocking the function of the BNST or the CeA resulted in a dramatic decrease in retreat behavior because the negative effects of the drug were blocked.

In the newly published paper, the researchers used drugs that selectively block the action of the neurotransmitter, noradrenaline, in the BNST and CeA rather than the entire function. The results were similar to those in the earlier study. “If you put norepinephrine antagonists directly into the BNST or the CeA, you can prevent or dramatically attenuate the negative effects of cocaine, leaving the positive effects

intact," Ettenberg explained. "So the animals show fewer retreats in the runway."

The study looked at acute cocaine use with only one injection a day, which is not considered a model of addiction. So the natural extension of this paper's line of inquiry is how the positive and negative systems associated with cocaine use change when animals are exposed to multiple doses in any given day (i.e. addiction). Subsequent studies have demonstrated that as the animals become addicted to the drug, the positive consequences get reduced and negative effects get exaggerated so the net experience is less positive. To overcome the decreased positive effects, users increase the dose, which creates a behavioral spiral.

"We need to more fully understand the underlying neuronal mechanisms altered by cocaine before we can treat people," Ettenberg said. "Once we understand how the brain systems producing the positive/euphoric and negative/anxiety effects of the drug interact, we might be able to produce treatments that address the balance between these two opposing actions, both of which serve as strong driving forces. We therefore need to understand both of these systems in order to come up with a rational treatment down the line."

About UC Santa Barbara

The University of California, Santa Barbara is a leading research institution that also provides a comprehensive liberal arts learning experience. Our academic community of faculty, students, and staff is characterized by a culture of interdisciplinary collaboration that is responsive to the needs of our multicultural and global society. All of this takes place within a living and learning environment like no other, as we draw inspiration from the beauty and resources of our extraordinary location at the edge of the Pacific Ocean.