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Behavioral flexibility impaired after exposure to oxycodone

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Brief usage of the painkiller oxycodone may impair behavioral flexibility even after that use ends, suggesting impaired decision-making as an enduring consequence of exposure, according to a study conducted at the Icahn School of Medicine at Mount Sinai and published November 17 in the journal *Learning and Memory*.

The Mount Sinai study investigated behavioral flexibility, the ability to select new responses when otherwise familiar circumstances change. In people and rodents exposed to drugs of addiction, repeated actions can become automated and resistant to change. While habits can be useful because practiced actions enable quicker achievement of some goals, habits can also cause harm when they persist despite worsening consequences. Drug habits represent extreme cases of reduced behavioral flexibility.

Drugs of abuse cause widespread cellular and molecular changes in brain circuitry, including prefrontal regions involved in behavioral flexibility. While previous studies found that behavioral flexibility is impaired in human addicts and animals exposed to extended dosages of cocaine and amphetamine, the effects of a typical dose of oxycodone, a commonly prescribed opiate pain medication with high abuse liability, had not been systematically explored.

"Oxycodone binds to opiate receptors that are distributed throughout brain systems involved in important learning and memory processes," says Katharine M. Seip-Cammack, postdoctoral fellow and lead author

of the study. "Our data suggests that even relatively limited exposure to oxycodone can impair how these brain circuits are able to guide behavior. These impairments affect decision-making and could be one reason why people continue to use or abuse the drugs, long after they are medically necessary."

Specifically, using rats exposed to five days of relatively mild doses of oxycodone, comparable to what is prescribed to alleviate post-surgical pain in humans, researchers discovered that days after the drug exposure had ended, the rats tested in a drug-free state responded in more rigid, maladaptive ways, suggesting that impaired cognitive flexibility is an enduring consequence of oxycodone exposure.

Decision-making is based on computing the outcome of actions and is informed by both habits and recent memory (episode), each of which is "learned" by different memory systems in the brain, according to the study authors. Episodic memory requires the hippocampus, a brain structure deep in the cortex, whereas learning of habits (i.e. riding a bike) requires the striatum, a subcortical structure. A healthy brain integrates memories and habits with the outcome of choice to guide adaptive decision-making. This integration is necessary since changing situations require behavioral flexibility. If the brain has endured prefrontal cortical damage caused by drug exposure, however, habits and recent memories are available but flexibility to new situations is still impaired.

The research study, led by Matthew Shapiro, PhD, Professor of Neuroscience at the Icahn School of Medicine at Mount Sinai, compared the effects of oxycodone exposure on recent memory, established habits and behavioral flexibility. Using a series of learning and memory tasks that engage distinct learning strategies and brain circuits, the rats were tested in a series of experiments: initial learning of a maze discrimination task, a memory retention test, either oxycodone or saline

exposure for five days, a post-drug reminder (memory) test and subsequent spatial memory and motor habit tests. Using chocolate sprinkles as the changing reward contingency, researchers found that behavioral flexibility was impaired in tasks that require recent memory and hippocampal function as well as in tasks based on habits and striatal function days after drug exposure when the rats were in a drug-free state. They also found that not all of the rats treated with oxycodone were strongly impaired - some learned the new maze changes normally.

"Our data imply that oxycodone treatment may lead to enduring brain changes that impair behavioral flexibility and decision-making, a 'cognitive hangover' that may contribute to the process of drug addiction," says Dr. Shapiro. "The range of cognitive effects in different individuals can guide future experiments on addiction. Perhaps the degree of 'cognitive hangover' helps explain why only some animals (and people) given a standard oxycodone treatment develop drug habits."

Provided by The Mount Sinai Hospital

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