Genetically altered mice no longer like cocaine

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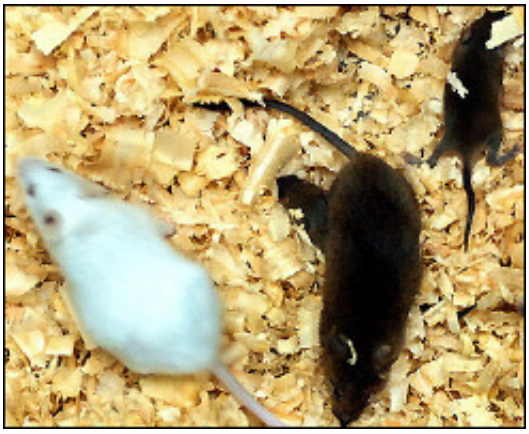

Researchers found that they could eliminate the rewarding effect of cocaine on mice by genetically manipulating a key target of the drug in the animal's brain.

While the researchers aren't suggesting that these genetic modifications be made in humans, the work brings to light the key protein that controls cocaine's effects in the body, which may help scientists develop medications that achieve the same results and therefore help addicts overcome their dependence.

Right now there are no such treatments on the market, said Howard Gu, the study's lead author and an associate professor of pharmacology and

psychiatry at Ohio State University .

The study confirms that the dopamine transporter – a protein that moves the neurotransmitter dopamine from outside of a neuron into the inside of the cell – is a prime target for developing drugs to fight cocaine addiction.

“Cocaine blocks dopamine transporters, and this action ultimately is what makes a person feel high,” Gu said. “We found that cocaine would not produce a high if it could not block the transporters.”

He and his colleagues reported their findings the week of May 29 in the Proceedings of the National Academy of Sciences.

Dopamine is a chemical messenger vital to the regular functioning of the central nervous system. Under normal circumstances it flows into and out of neurons.

But cocaine blocks dopamine transporters from taking up dopamine, leaving it outside the cells, which excites the nervous system to the point where a cocaine user feels a high, Gu said.

He and his colleagues raised laboratory mice with genetic alterations in the gene that codes for the dopamine transporter.

“By doing so we created a dopamine transporter that resists cocaine but also retains its function of taking up dopamine and carrying it back to the neurons,” Gu said.

The researchers tested cocaine's effects on normal mice and on mice with modified dopamine transporters. The animals received varying amounts of cocaine. Some mice from both groups – the normal mice and the animals with modified transporters – served as controls and were

given only saline injections throughout the experiment.

Individual mice were placed in a 5-inch-by-7-inch acrylic box with three compartments – a middle compartment and two test compartments. On the first day of the experiment, mice were allowed to roam around the box.

During the next several days, mice received injections of saline and then various amounts of cocaine on alternating days. Mice injected with saline were confined in one test compartment, while mice injected with cocaine were confined to the other compartment. Mice were kept in these respective compartments for 30 minutes. On the last day of the experiment, mice were again free to roam the box, and no injections were given. The animals were videotaped while they were in the box.

“The normal mice spent more time in the compartment where they had received the cocaine injections,” Gu said. “These animals were seeking more cocaine. However, the mice with the modified transporters showed no preference for either test compartment within the box.”

The researchers used the video footage to measure each animal's activity level after a cocaine injection. The normal mice on cocaine covered roughly five times the distance than the control mice injected with saline (6 meters vs. 1 meter). In contrast, the cocaine-injected mice with the modified dopamine receptors covered about half the distance that the saline-only injected mice covered (roughly 1.5 meters vs. 3 meters.)

“After the cocaine injections, the normal mice ran all over the place, sniffing and checking everything out in the box over and over again, until we took them out of the box,” Gu said. “But cocaine seemed to calm the modified mice, as they sat in a corner for long periods of time.”

“To the modified mice, cocaine appears to be a suppressant, not a

stimulant," Gu said.

In previous work, other scientists studied mice that lacked a dopamine transporter. Since cocaine's key target was missing in these mice, the researchers thought that the drug wouldn't trigger a high. They were wrong. This led to the proposal that there may be redundant reward pathways for cocaine reward.

"Deleting the dopamine transporter itself caused tremendous changes in the mouse brain," Gu said. "It's possible that, somehow, the animals' brains rewired themselves and, as a result, the mice still felt the effects of cocaine."

The current study suggests that cocaine's blockade of dopamine transporters is still required in order to produce a high in normal mice.

Gu said the next step is to screen for compounds that could produce the same effect that the genetic modifications did in this study.

"We hope to find certain drugs that prevent cocaine from binding to transporters, but that still allow the transporter protein to carry the dopamine back to the neuron," he said.

Source: Ohio State University