Nicotine and cocaine leave similar mark on brain after first contact

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The effects of nicotine upon brain regions involved in addiction mirror those of cocaine, according to new neuroscience research.

A single 15-minute exposure to nicotine caused a long-term increase in the excitability of neurons involved in reward, according to a study published in The *Journal of Neuroscience*. The results suggest that nicotine and cocaine hijack similar mechanisms of memory on first contact to create long-lasting changes in a person's brain.

"Of course, for smoking it's a very long-term behavioral change, but everything starts from the first exposure," said Danyan Mao, PhD, postdoctoral researcher at the University of Chicago Medical Center. "That's what we're trying to tackle here: when a person first is exposed to a cigarette, what happens in the brain that might lead to a second cigarette?"

Learning and memory are thought to be encoded in the brain via synaptic plasticity, the long-term strengthening and weakening of connections between neurons. When two neurons are repeatedly activated together, a stronger bond forms between them, increasing the ability of one to excite the other.

Previous research in the laboratory of Daniel McGehee, PhD, neuroscientist and associate professor in the Department of Anesthesia & Critical Care at the Medical Center, discovered that nicotine could promote plasticity in a region of the brain called the ventral tegmental

area (VTA). Neurons that originate in the VTA release the neurotransmitter dopamine, known to play a central role in the effects of addictive drugs and natural rewards such as food and sex.

"We know that a single exposure to physiologically relevant concentrations of nicotine can lead to changes in the synaptic drive in the circuitry that lasts for several days," said McGehee, senior author of this study. "That idea is very important in how addiction forms in humans and animals."

In the new experiments, Mao monitored the electrical activity of VTA dopamine neurons in slices of brain dissected from adult rats. Each slice was bathed for 15 minutes in a concentration of nicotine similar to the amount that would reach the brain after smoking a single cigarette. After 3-5 hours, Mao conducted electrophysiology experiments to detect the presence of synaptic plasticity and determine which neurotransmitter receptors were involved in its development.

Mao discovered that nicotine-induced synaptic plasticity in the VTA is dependent upon one of the drug's usual targets, a receptor for the neurotransmitter acetylcholine located on the dopamine neurons. But another element found necessary for nicotine's synaptic effects was a surprise: the D5 dopamine receptor, a component previously implicated in the action of cocaine. Blocking either of these receptors during nicotine exposure eliminated the drug's ability to cause persistent changes in excitability.

"We found that nicotine and cocaine employ similar mechanisms to induce synaptic plasticity in dopamine neurons in VTA," Mao said.

While the subjective effects of nicotine and cocaine are very different in humans, the overlapping effects of the two drugs on the reward system of the brain may explain why both are highly addictive substances, the

researchers said.

"We know without question that there are big differences in the way these drugs affect people," McGehee said. "But the idea that nicotine is working on the same circuitry as cocaine does point to why so many people have a hard time quitting tobacco, and why so many who experiment with the drug end up becoming addicted."

The overlap between nicotine and cocaine effects at the D5 receptor may also offer a novel strategy for preventing or treating addiction. However, currently-known blockers of the receptor also block another dopamine receptor, D1, that is important for normal, healthy motivation and movement.

"This dopamine receptor is attractive as a potential target," McGehee said. "The real challenge is to tweak the addictive effect of drugs like nicotine or other psychostimulants without totally crushing the person's desire to pursue healthy behavior."

Future research will also focus on whether repeated exposure to nicotine, as would occur in a regular smoker, changes the drug's effects on synaptic plasticity in the VTA. In the meantime, the current study builds evidence that addictive drugs appropriate the neurobiological tools of learning and memory to create long-term changes in brain reward pathways.

"It's all fitting with the overriding idea that changes in synaptic strength are part of the way these drugs motivate behavior in a persistent way," McGehee said.

More information: The study, "Nicotine Potentiation of Excitatory Inputs to Ventral Tegmental Dopamine Neurons," will be published May 4, 2011 by The Journal of Neuroscience.

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