New study: Flipping molecular 'switch' may reduce nicotine's effects in the brain

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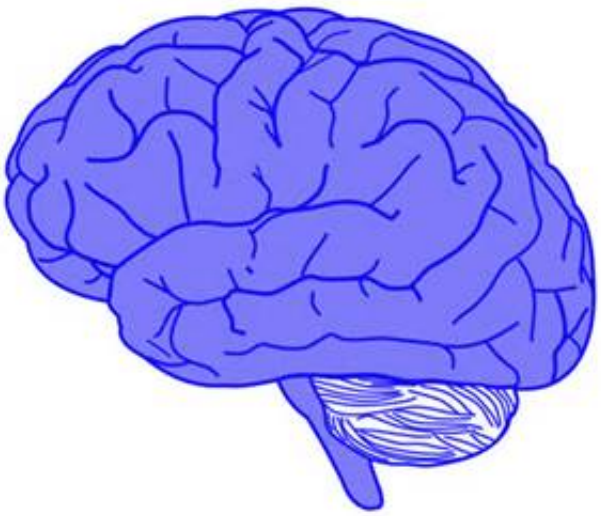

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January 13, 2016 - Scientists at The Scripps Research Institute (TSRI) have discovered that a lipid (fat molecule) in brain cells may act as a "switch" to increase or decrease the motivation to consume nicotine.

The team's findings in animal models point to a way that a drug might someday return this lipid to normal levels, perhaps making it easier for smokers to quit.

"We knew these lipids were implicated in nicotine addiction, but until now manipulating their synthesis was not pharmacologically feasible," said TSRI Professor Loren ("Larry") Parsons, senior author of the new study, which involved a close collaboration with the TSRI labs of Professor Marisa Roberto and Benjamin F. Cravatt, chair of the Department of Chemical Physiology and member of the Skaggs Institute for Chemical Biology at TSRI.

The study was published this week in the journal *Proceedings of the National Academy of Sciences.*

How Nicotine Changes the Brain

The motivation for natural rewards such as food, sex and exercise—and also of drugs such as nicotine —relies on neurons in the brain's reward system, based in a brain region called the ventral tegmental area (VTA). Obtaining a reward leads to excitation of these neurons and the release of a neurotransmitter called dopamine, which acts on other neurons to trigger positive emotions.

The degree to which the reward system can be activated is normally tightly controlled. A neurotransmitter called GABA (gamma aminobutyric acid) inhibits excitatory signaling in neurons and keeps the system in balance.

Chronic nicotine exposure sabotages this carefully balanced system. Previous research indicated that chronic nicotine exposure boosts the excitation of dopamine signaling while decreasing the controls on this system by GABA's inhibitory signaling. "This is thought to contribute in part to the motivation for continued nicotine use," explained Parsons.

Dopamine doesn't act alone. Nicotine exposure also leads to the release of lipids called endocannabinoids, which affect dopamine-producing

neurons. Because of this, some researchers have tested potential anti-smoking therapies that block activity in the endocannabinoid receptor, where endocannabinoids bind. These treatments reduced the effects of nicotine on dopamine release and tended to reduce smoking.

"Unfortunately these treatments also produced undesirable side effects, like depression and anxiety, that limited their clinical use," said TSRI Research Associate Matthew Buczynski, who was co-first author of the study with Melissa A. Herman, senior research associate in the Roberto lab, and Ku-Lung Hsu, who was a research associate at TSRI at the time of the study and is currently an assistant professor at the University of Virginia.

The team hypothesized that instead of blocking endocannabinoid receptors throughout the brain, it would be more effective to specifically target the endocannabinoid mechanism that appears to be dysregulated by chronic nicotine.

Restoring the Brain's Balance

The new study suggests compounds called 1,2,3-triazole urea (TU) inhibitors can block the production of a specific endocannabinoid called 2-arachidonoylglycerol (2-AG).

These inhibitors were selected by Hsu for their potential to inhibit the source of 2-AG itself: an enzyme called diacylglycerol lipase. Next, Herman led studies of the cellular effects of chronic nicotine exposure on GABA signaling in rat brains. These experiments revealed a strong correlation between enhanced production of 2-AG by diacylglycerol lipase and decreased GABA levels. The team then targeted the 2-AG pathway using the 1,2,3-TU inhibitors characterized by Hsu.

"This research was a real team effort, and the quality of the science

reflects the respective strengths of the team," said Herman.

The researchers found that in animal models with a history of nicotine exposure, GABA signaling returned to normal when the effects of nicotine on 2-AG production were prevented with the 1,2,3-TU inhibitors. Blocking 2-AG production also affected the motivation to consume nicotine. Buczynski observed that treating rats with the 1,2,3-TU inhibitors reduced voluntary nicotine self-administration without changing the motivation for natural rewards (for example, water self-administration by thirsty rats).

"This suggests 2-AG acts as a molecular switch for turning an important inhibitory control of dopamine neurons on and off," said Buczynski. If this switch is turned off, as in those with chronic nicotine exposure, the excitation of dopamine neurons by nicotine is less controlled, and the drug is more rewarding.

The findings could guide future therapies, perhaps enabling scientists to design therapeutics that prevent aberrant 2-AG activity without affecting other healthy activity at the endocannabinoid receptor.

The study also opens a door to new basic research, noted Parsons. Because endocannabinoids influence many aspects of behavior, inhibitors similar to 1,2,3-TU compounds may be the key to investigating normal brain function.

More information: Matthew W. Buczynski et al. Diacylglycerol lipase disinhibits VTA dopamine neurons during chronic nicotine exposure, *Proceedings of the National Academy of Sciences* (2016). DOI: 10.1073/pnas.1522672113

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