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Researchers identify neurobiological mechanism underlying nicotine withdrawal symptoms

TORONTO, Canada—The craving for nicotine experienced by smokers trying to kick their habit—and which pushes many to relapse—is in part the result of specific patterns of dopamine neuronal activity, according to new research from the University of Toronto, done in collaboration with The Scripps Research Institute and the University of Western Ontario.

Dopamine is a brain chemical, critical to mood, which plays a role in drug addiction, Parkinson's disease, schizophrenia and other conditions. The researchers showed that nicotine withdrawal is characterized by decreased activity in "tonic" chemical receptors, which provide baseline, routine signaling in the brain, as opposed to activity in "phasic" receptors, which respond to brain stimulation.

"Modifying specific tonic dopamine receptors could potentially be a therapeutic treatment for nicotine addiction," said Taryn Grieder, lead author on the study. Grieder is an Institute of Medical Science doctoral student in the lab of Prof. Derek van der Kooy, a Professor in U of T's Department of Molecular Genetics who is based at the Terrence Donnelly Centre for Cellular and Biomolecular Research.

The *Proceedings of the National Academy of Sciences* published the research findings.

The researchers tested the effects of withdrawal by performing electrophysiological recordings of the ventral tegmental area—a group of neurons located close to the midline on the floor of the midbrain—in rodents that were either drug-free or nicotine dependent and in withdrawal.

The team's experiments included blockade of neuronal activity through genetic modification and pharmacological means, through which they showed that tonic receptors mediate the body's response to chronic nicotine intake and withdrawal. Sudden acute exposure to nicotine, they also showed, is mediated by phasic receptors.

"The really interesting finding here is that the two different types of receptor activity are important depending on whether the subject is experiencing nicotine withdrawal or not," said Grieder. "New drugs that modify the brain's tonic receptor activity during nicotine withdrawal, and possibly during withdrawal from other drugs of abuse as well, may prevent the negative feelings associated with it."

The research was funded by the Canadian Institutes of Health Research, National Institutes of Health, the State of California and the Pearson Center for Alcoholism and Addiction Research at The Scripps Research Institute.