Nicotine causes the neural circuits that control behavioral choice to change in a way that locks in smoking-related behaviors—making them difficult to unlearn.

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“We wanted to tease out different parts of addiction,” says lead author Boris Gutkin, PhD, a research scientist at the Pasteur Institute in Paris, France. “The goal is to put behavioral and neural information together and to see how the behavioral effects are produced by the neural effects.”

in the dopamine signal; medium-term production of more receptors, which further increases the dopamine signal; and long-term opponency, a process that attempts to bring the system back into balance by decreasing the amount of dopamine.

Combining these dopamine changes with a module that gave smokers a choice after each smoking session, the researchers asked, essentially, will this smoker choose to smoke again. They found that—especially after the second session—the model smoker consistently keeps smoking. The researchers suggest that the dopamine message (“nicotine is rewarding”) gets locked in neurally—and becomes hard to unlearn. Smokers continue to seek out nicotine even when the opponent process reduces the amount of dopamine in the system and the pleasure goes out of smoking. Moreover, when nicotine is withdrawn from a smoker, the researchers say, the dopamine-lowering opponent process is still in effect. As a result, dopamine levels drop below normal, and it’s hard to find pleasure in anything.

The researchers were most pleased by the observation that nicotine sensitizes the system to the dopamine response. That is, the response to the second dose of nicotine is bigger than to the first, and has a significant effect on the choices made (to smoke or not smoke), whereas the first dose did not—presumably because of the learning effect on the decision maker. Likewise, a smoker who quits and starts again does not start from zero, but learns to self-administer nicotine faster the second time.

A few things about nicotine addiction were already known. First, nicotine stimulates specific receptors on neurons that produce dopamine, causing them to produce more of this key neurotransmitter for motivation, reward and learning. Second, dopamine modifies learning in the circuits that are responsible for making choices. And third, nicotine results in addictive behavior. A wealth of behavioral data, including experiments in which rats are trained to self-administer nicotine, indicates that once a rat (or human) starts the habit, it will choose to continue. It will even learn to navigate complex mazes or press levers to obtain nicotine.

The model developed by Gutkin and his colleagues examines how a hypothetical animal “behaves” when given two choices: to smoke or not to smoke. “We found that simulation of both the biophysical effects of nicotine at the neuronal level and the subsequent effect on learning reproduced certain aspects of the behavioral data.”

In the biophysical part of the model, the researchers developed a simple kinetic scheme for how a population of neuronal receptors would react to nicotine on three different time scales: short-term stimulation of nicotinic receptors, leading to a burst of dopamine release; medium-term production of more receptors, which further increases the dopamine signal; and long-term opponency, a process that attempts to bring the system back into balance by decreasing the amount of dopamine.

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