Podcast interview: Inés Ibañez-Tallon

PNAS: I’m your host Nicholette Zeliadt, and welcome back to Science Sessions. It seems few habits are harder to kick than cigarette smoking. That’s in part because chronic exposure to nicotine, the addictive component of tobacco that acts by binding to so-called nicotinic acetylcholine receptors in the brain, alters neural circuits to promote addiction. In addition, smokers who attempt to quit frequently experience nicotine withdrawal symptoms, such as irritability, anxiety, and loss of concentration, that often promote relapse. A study published last October in PNAS sheds some light on the molecular mechanisms of nicotine withdrawal and relapse. In that paper, researchers reported the identification of a group of neurons that mount a heightened response to nicotine after a period of abstinence. The findings suggest that the altered activity of these neurons may undermine efforts to quit smoking. I recently sat down with the study’s corresponding author, Inés Ibañez-Tallon, a visiting professor in the Laboratory of Molecular Biology at the Rockefeller University in New York City, to discuss her team’s findings. She begins by describing the motivation for this work.

Ibañez-Tallon: There [are] 1 billion smokers in the world. And the main reason many smokers have a problem to quit is the relapse. So it has been shown that 90% of the smokers trying to quit fail. One of the difficulties to quitting smoking is the symptoms of withdrawal that develop—anxiety, irritability, problems with sleeping, problems with concentration. These symptoms are very pronounced during the first 3 months when a person is trying to quit.

PNAS: Previous studies had shown that the α3, β4, and α5 subunits of the nicotinic acetylcholine receptor play a key role in heavy tobacco use and relapse, but the molecular mechanisms have remained unclear. To better understand the neural signals that modulate nicotine cravings, the team compared the activity of neurons from two areas of the mouse medial habenula—a brain region where the α3, β4 and α5 receptor subunits are concentrated. They uncovered the presence of so-called pacemaker channels that promote rhythmic electrical pulses in the brain.

Ibañez-Tallon: What we found [was] that in normal conditions, these cholinergic neurons have spontaneous tonic firing, so they are always active, to a certain continuous level. But, upon nicotine treatment, they respond more, through these α3 β4 receptors, and the interesting thing was that, after a period of abstinence, when the mice start having withdrawal symptoms, short re-exposure to nicotine, increases much more these levels. Sort of, the neuron remembers how good it was, the nicotine, in a way. It’s a little bit reminiscent, if you interview smokers, the best cigarette of the day is the first cigarette in the morning. And, not only after 8 hours, but in withdrawal, so after 3 days, and this is maintained during a critical time, if by chance, you smoke a cigarette because you cannot take the withdrawal in this short period, these neurons remember, and you will most likely start smoking again because it felt much higher.

PNAS: I asked Ibañez-Tallon how long the neurons “remember” nicotine, and display a heightened response to the substance.

Ibañez-Tallon: We are trying to understand this, if there is sort of a mechanism, a memory, we know it lasts for at least a week. And we’re trying to see if we can enhance this period, making it
shorter, or understand what is lasting in the absence of nicotine, to understand how we can avoid this enhanced response that will make the relapse much more probable.

**PNAS:** The findings, while preliminary, may have important implications for developing strategies to help people quit smoking.

**Ibañez-Tallon:** Smoking is a very complex biological problem. There’s addiction, but there’s also the whole brain readapts to the presence of nicotine, so there is a component of withdrawal, there’s a component of reward, and there’s a component of cognition, or positive behavior. So it’s very difficult to think therapeutically about something that will finally eradicate smoking in the world. It’s very difficult to affect reward, because that will be reward to anything that gives us reward. Cognition you can do positive behavior, but the withdrawal, I think this gives us an insight into, if we can make the withdrawal severity less, it could increase the possibility to quit smoking. What is difficult is that the therapeutical drugs that would be applied can’t target nicotinic receptors because they are so present in different areas of the brain and the body. So I think we have to understand more of the complexity and the mechanisms to find more targeted molecules that do exactly one little part of the withdrawal mechanism.

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