Parental nicotine use and addiction risk for children

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In the United States in 2021, about one in every 50 high school students reported smoking a cigarette in the past month, according to the National Youth Tobacco Survey. For the same time frame, that number jumped

to one in nine for e-cigarettes.

Most smokers form this habit before age 25. Previous research has offered some explanation, including a link between parents who smoke and the addiction risk of their children. Heath Schmidt, a neuroscientist in Penn Nursing, wanted to better understand this connection.

"There's plenty of epidemiological data to indicate that the offspring of parents who smoke tobacco products will go on to develop or be at higher risk for developing nicotine dependence," says Schmidt, an associate professor of nursing and psychiatry. "There's a lot to suss out in all of that."

Schmidt studies what happens in the brain during addiction, aiming to parse why addictive behaviors come to pass and how treatment options might improve. In this latest work, he and colleagues from Penn's School of Nursing and Perelman School of Medicine, Temple University, and the Robert Wood Johnson Medical School at Rutgers wanted to determine the heritable effects of paternal exposure to nicotine.

Using a novel rat animal model, the researchers found that males that voluntarily self-administered nicotine for 60 days produced offspring more likely to self-administer nicotine, too. This was true for both male and female young. The team also discovered that the male offspring of these parents developed impaired memory and anxiety-like behavior.

The researchers published their findings in the journal *Molecular Psychiatry*. Penn Today spoke with Schmidt about the work and its implications.

What motivated this particular study?

This idea of looking at how environmental stimuli can impact future

generations has been a growing field in the past decade. This particular work derived from other studies I'd done with colleagues focused on cocaine, not on nicotine.

Previous research has shown a link between parents who smoke or use tobacco products and an increased risk of addiction in their children?

There are data that do indicate that both the sons and daughters of parents who smoke will go on to develop a nicotine-use disorder. There's some evidence that they might develop cognitive impairment as well. But we don't yet know why.

We have some guesses. Children who grew up in households where smoking is a regular part of their daily lives see it. It's a behavior that they may model. It's not necessarily clear whether that's due to a direct impact of nicotine itself on the developing embryo. The real benefit of the animal model is we can hone in on the effects of the drug itself on offspring development and physiology.

What was the main finding of your research here?

The major findings were that both the male and female offspring of the fathers that consumed the nicotine had enhanced nicotine-taking. That fits with the human data out there, that the offspring of fathers who smoke tobacco products are more susceptible to developing a nicotine-use disorder.

We also saw sex-dependent effects where the male, but not female, offspring developed cognitive deficits, as well as anxiety-like behavior. Those are consistent with the previous models, too. Cognitive deficits like this are mediated by the hippocampus, an area in the brain that

regulates learning and memory, so we decided to look at genes to determine which were involved. One stood out, Satb2.

What is Satb2?

It's a gene that plays a role in neurodevelopment, in the developing brain, but not much is known about its role in the adult brain. Two recent studies showed that Satb2 plays a role in the synaptic plasticity in the hippocampus, as well as learning and memory in the adult brain. We thought that fit perfectly with what we were seeing.

What did you find when you dug deeper into Satb2?

We saw that these male offspring with cognitive deficits had decreased levels of Satb2 in the hippocampus. That really supported the hypothesis that decreases in Satb2 underlie these cognitive deficits. The obvious next step was to try to reverse that decrease, so we developed a virus that would over-express Satb2 in the hippocampus.

With elevated levels of Satb2 in the hippocampus, we found that we could prevent or reverse the cognitive deficits in the nicotine-sired male offspring. That was really encouraging. We also looked at the increase in nicotine-taking we saw in the male offspring; we found that this enhanced Satb2 expression also normalized it, brought it back to normal levels. So, it seems to play a role in both behaviors we found in this study.

Given that you conducted this work using an animal model, what are the implications for addiction risk in humans?

Speaking broadly, pre-clinical studies like this shine a spotlight on the

ongoing issues that we have with nicotine consumption. They highlight vulnerable populations; we show that the sons and daughters of fathers who smoked tobacco cigarettes or electronic cigarettes may be vulnerable populations. They're potentially at risk of developing nicotine-use disorders themselves. They're potentially at risk for developing cognitive deficits. There's a higher incidence of ADHD of offspring of parents who have smoked tobacco products.

I also think it provides us some new insights into phenotypes that we might see in young children and adolescents of parents who consumed drugs of abuse. It potentially offers novel ways to look at these behaviors and how to treat them. That's the ultimate goal—and possibly far-reaching at this point—but I think our model and the data support that type of approach.

More information: John J. Maurer et al, Paternal nicotine taking elicits heritable sex-specific phenotypes that are mediated by hippocampal Satb2, *Molecular Psychiatry* (2022). DOI: 10.1038/s41380-022-01622-7

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