The Science of Tobacco Addiction and Cessation

Understanding the molecular basis of nicotine dependence will inform strategies to stop smoking

Smoking dramatically increases the risk for lung cancer, chronic obstructive pulmonary disease, and other medical conditions, but most smokers simply can’t break free from tobacco on their own. More than 85% relapse, usually within a week.

“Smokers have this feeling that they aren’t successful because they weren’t strong enough or didn’t have enough willpower,” says Laura Bierut, MD, professor of psychiatry at Washington University School of Medicine in St. Louis, MO.

Over the past decade, however, researchers have found genetic variations that affect how nicotine, the main addictive component of tobacco, interacts with cells in the brain and how fast the body metabolizes it. In both cases, carrying a high-risk variant predicts a person’s ability to snuff out their cigarettes for good. “If we identify those people and let them know it’s not a moral failing on their part, that they’re not weak and that it’s not a question of willpower, but a question of biology, that could actually be very powerful,” says Bierut.

Genetic profiles could predict which smokers might benefit from nicotine replacement therapy (NRT) or the prescription medications bupropion (Zyban; GlaxoSmithKline) and varenicline (Chantix; Pfizer). As with cancer treatment, “this is a poster child for what personalized medicine could be,” comments Bierut.

BECOMING ADDICTED

Within seconds of inhalation, nicotine interacts with nicotinic acetylcholine receptors on brain cells that release dopamine, explains psychologist Caryn Lerman, PhD, deputy director of the Abramson Cancer Center at the University of Pennsylvania in Philadelphia. Dopamine levels rapidly increase, causing feelings of pleasure and reward. Nicotine’s effects, however, are short-lived and may be followed by symptoms of withdrawal such as irritability, cravings, anxiety, increased appetite, cognitive and attention deficits, and trouble sleeping.

Over time, Lerman continues, the number of nicotine receptors on brain cells can increase, further driving the craving for nicotine. In addition, nicotine exposure can cause neurochemical changes affecting how different parts of the brain connect with each other. For example, when certain activities are regularly paired together, such as drinking coffee and smoking a cigarette, certain neurons will fire together.

“Neurons that fire together, wire together,” says Lerman, so merely having one’s usual cup of coffee could induce a cigarette craving.

The reason some people have so much trouble breaking the addiction while others don’t wasn’t really understood until genetic breakthroughs were reported in the mid-to late 2000s. In 2008, multiple research teams uncovered genetic variations in CHRNA5, CHRNA3, and CHRNA4, genes that code for subunits of nicotinic acetylcholine receptors on neurons in the brain. Carrying a high-risk variant seems to influence how heavily a person will smoke, how addicted to nicotine that person will become, and how likely that person is to relapse after attempting to quit, the researchers discovered.

About 16% of smokers have two high-risk variants, says Bierut, while roughly 40% have one high-risk variant.

In 2012, Bierut and her Washington University colleague Li-Shiun Chen, MD, MPH, ScD, an assistant professor of psychiatry, along with researchers from the University of Wisconsin in Madison and other institutions, built on earlier work using data from 1,073 participants in a randomized, placebo-controlled smoking cessation trial. They found that smokers with the high-risk variants were three times more likely than smokers with a low-risk genetic variant to respond to pharmacologic cessation therapies—nicotine patches, nicotine lozenges, or bupropion alone, or combinations of patches and lozenges or lozenges and bupropion (Am J Psychiatry 2012;169:735–42).

Variants in another gene, CYP2A6, identified over the last decade affect the rate of nicotine metabolism, studies have shown. About 70% of smokers have a gene variation that causes them to metabolize nicotine quickly, while the rest metabolize it more slowly.

In a study published online in November, Chen, Bierut, and their colleagues studied 709 smokers to assess the impact of CYP2A6 on smoking-cessation success and response to pharmacotherapy (Addiction 2014;109:128–37). Participants were randomly assigned to receive a placebo, NRT, bupropion, or a combination of bupropion and NRT for 8 weeks.

The team found that one third of fast nicotine metabolizers responded to NRT, but slow metabolizers did not respond, suggesting that they should try other therapies instead. In addition, they discovered that CYP2A6 could not predict whether a smoker would respond to treatment with bupropion.

Available $\beta^+$-nicotinic acetylcholine receptors

The number of $\beta^+$-nicotinic acetylcholine receptors is elevated in the brain in male smokers, promoting nicotine cravings. As they abstain from nicotine, the brain eliminates the receptors. After 6 to 12 weeks of abstinence, the number of receptors returns to levels seen in nonsmokers. [Image based on illustration from the National Institute on Drug Abuse.]
A NICOTINE VACCINE?

Given that long-term smoking abstinence rates rarely exceed 30%, some researchers are trying to develop vaccines that create antibodies that bind to nicotine in the bloodstream and prevent it from entering the brain.

“Conceptually, the nicotine vaccine is a good idea because it just targets the nicotine molecule, so it doesn’t have the side effects that other medications have,” says Dorothy Hatsukami, PhD, a professor of psychiatry at the University of Minnesota in Minneapolis.

“In fact, animal studies and some of our earlier human studies have shown that if there are high enough levels of antibodies in the system, there will be more success in reducing nicotine self-administration in animals and quitting smoking in humans,” Hatsukami adds.

Hatsukami led successful phase II studies of one vaccine, NicVAX, developed by Nabi Pharmaceuticals.

Fast metabolizers are more likely to relapse when they try to quit, explains Chen, “because when their nicotine levels drop rapidly, they can fall victim to cravings.” The good news, she says, is that NRT seems to even out their nicotine levels and control their cravings.

Chen says her team’s next step is to examine the interplay between CHRNA5, which codes for a subunit of nicotinic acetylcholine receptors, and CYP2A6, as well as the genes’ overall effects on smoking cessation and treatment with NRT or bupropion. Extensive studies have not been done with varenicline, but because it is a nicotinic agonist, Bierut expects that it may work much like NRT.

GENDER DIFFERENCES AT PLAY

Research sponsored by the National Institute on Drug Abuse suggests that men may benefit more from NRT than women. Kelly Cosgrove, PhD, an associate professor of psychiatry and diagnostic radiology, and colleagues at Yale University School of Medicine in New Haven, CT, conducted single-photon emission computed tomography (SPECT) scanning of the brain in 26 male and 28 female smokers after 7 to 9 days of abstinence, and 26 male and 30 female nonsmokers.

The comparison revealed that male smokers had a significantly higher number of β2*-nicotinic acetylcholine receptors than male nonsmokers throughout the cortex, cerebellum, and striatum, but not the thalamus (Arch Gen Psychiatry 2012;69:418–27). In contrast, female smokers had fewer β2*-nicotinic acetylcholine receptors in the thalamus than female nonsmokers, but similar numbers of receptors in other brain regions.

The findings offer a biologic basis for different responses to cessation therapy between the sexes: Men, who generally smoke more for nicotine reinforcement, often get more relief from NRT than women, says Cosgrove. Women, on the other hand, seem to smoke more to regulate stress and in response to environmental cues, she says. The thalamus, where women showed changes in β2*-nicotinic acetylcholine receptors, aids in the flow of sensory information between the cortex and areas of the brain associated with emotion.

“We really don’t know why the levels are lower in the thalamus in female smokers or why women do not have the expected upregulation of receptors seen in male smokers,” says Cosgrove, adding that it can take 12 weeks without nicotine for receptor numbers in former smokers to match those of nonsmokers.

The findings also suggest that “the way we’re treating addiction is not good enough,” especially among women, who seem to be more likely to relapse in response to stressful events, environmental triggers, and social cues, adds Cosgrove. “We need to develop approaches to cessation that target other types of receptors and do not rely on nicotine-containing therapies.”

Thanks to an improved understanding of the neurobiology of addiction, the development of non–nicotine-containing and new targeted therapies to aid cessation efforts is now possible. “The hope is that, in the same way that this happens with cancer, you could in the future combine genetic factors, other metabonomic measures, and neuroimaging measures to identify the best therapy for an individual smoker,” sums up Lerman. “The understanding of the basic science is moving us in the direction of not only developing better treatments, but also targeting the treatments that we do have more effectively.” –Suzanne Rose

This article is being published as part of the AACR’s commemoration of the 50th Anniversary of the Surgeon General’s Report on Smoking and Health. You are encouraged to visit http://www.aacr.org for information on additional AACR publications and activities related to the recognition of this important anniversary.
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Updated version
Access the most recent version of this article at:
doi:10.1158/2159-8290.CD-ND2013-029

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