Scientists reveal key mechanism governing nicotine addiction

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Scientists from the Florida campus of The Scripps Research Institute have identified a pathway in the brain that regulates an individual's vulnerability to the addictive properties of nicotine. The findings suggest a new target for anti-smoking therapies.

The study appeared January 30, 2011, in an advance, online issue of the journal *Nature*.

In the study, the scientists examined the effects of a part of a receptor (a protein molecule to which specific signaling molecules attach) that responds to nicotine in the brain. The scientists found that animal models with a genetic mutation inhibiting this receptor subunit consumed far more nicotine than normal. This effect could be reversed by boosting the subunit's expression.

"We believe that these new data establish a new framework for understanding the motivational drives in nicotine consumption and also the brain pathways that regulate vulnerability to tobacco addiction," said Scripps Research Associate Professor Paul Kenny, who led the study. "These findings also point to a promising target for the development of potential anti-smoking therapies."

Specifically, the new study focused on the nicotinic receptor subunit α5, in a discrete pathway of the brain called the habenulo-interpeduncular tract. The new findings suggest that nicotine activates nicotinic receptors containing this subunit in the habenula, triggering a response that acts to

dampen the urge to consume more of the drug.

"It was unexpected that the habenula, and brain structures into which it projects, play such a profound role in controlling the desire to consume nicotine," said Christie Fowler, the first author of the study and research associate in the Kenny laboratory. "The habenula appears to be activated by nicotine when consumption of the drug has reached an adverse level. But if the pathway isn't functioning properly, you simply take more. Our data may explain recent human data showing that individuals with genetic variation in the α5 nicotinic receptor subunit are far more vulnerable to the addictive properties of nicotine, and far more likely to develop smoking-associated diseases such as lung cancer and chronic obstructive pulmonary disease."

A Previously Unknown Pathway Inhibits Motivation

Tobacco smoking is one of the leading causes of death worldwide, with more than five million people dying each year as a result of it, according to statistics cited in the study. Smoking is considered the cause of more than 90 percent of lung cancer deaths. Scientists have established that a tendency towards smoking can be inherited – more than 60 percent of the risk of becoming addicted to nicotine can be laid at the door of genetic factors.

Nicotine is the major addictive component of tobacco smoke, and nicotine acts in the brain by stimulating proteins called nicotinic acetylcholine receptors (nAChRs). These nAChRs are made up of different types of subunits, one of which is the α5 subunit—the focus of the new study.

In their experiments, the Scripps Research scientists set out to determine the role of nAChRs-containing α5 subunits (α5* nAChRs) in regulating nicotine consumption.

First, the team assessed the addictive properties of nicotine in genetically altered mice lacking α5* nAChRs. The results showed that when these "knockout" mice were given access to high doses of nicotine, they consumed much larger quantities than normal mice. Next, to determine if the subunit was responsible for the sudden shift in appetite for nicotine, the scientists used a virus that "rescued" the expression of α5* nAChRs only in the medial habenula and areas of the brain into which it projects. The results showed the nicotine consumption patterns of the knockout mice returned to a normal range.

The scientists repeated the experiments with rats and produced similar results. In this case, the scientists used a virus to "knock out" α5 nAChR subunits in the medial habenula. When the α5* nAChRs were decreased, the animals were more aggressive in seeking higher doses of nicotine. When the subunit remained unaltered, the animals showed more restraint.

The scientists then worked out the biochemical mechanisms through which α5* nAChRs operate in the medial habenula to control the addictive properties of nicotine. They found that α5* nAChRs regulate just how responsive the habenula is to nicotine, and that the habenula is involved in some of the negative responses to nicotine consumption. So when α5* nAChRs do not function properly, the habenula is less responsive to nicotine and much more of the drug can be consumed without negative feedback from the brain.

The scientists are optimistic that their findings may one day lead to help for smokers who want to kick the habit. Based on the new findings, the Scripps Florida scientists have started a new program of research in collaboration with scientists at the University of Pennsylvania to develop new drugs to boost α5* nAChR signaling and decrease the addictive properties of nicotine.

Provided by The Scripps Research Institute