MedicalXpress

Scientists design nicotine vaccine that provokes robust immune response

January 12 2015

When a promising nicotine vaccine failed in clinical trials a few years ago, scientists from The Scripps Research Institute (TSRI) were determined to keep trying to help smokers overcome their addiction.

Now the team has designed a more effective nicotine vaccine and proven that the structures of molecules used in vaccines is critical. The study was published recently in the *Journal of Medicinal Chemistry*.

"This study provides new hope that one could make a nicotine vaccine that succeeds in clinical trials," said Kim Janda, the Ely R. Callaway Jr. Professor of Chemistry and member of the Skaggs Institute for Chemical Biology at TSRI.

Targeting Nicotine

According to the National Cancer Institute, smoking is the leading cause of eight types of cancer, including lung cancer and fast-moving pancreatic cancer.

Nicotine vaccines train the body to see nicotine as a foreign invader. To prompt this immune response, scientists have tried attaching nicotine derivatives called haptens to a larger carrier protein used in other approved vaccines.

The body reacts to the vaccine by creating antibodies to bind specifically

to nicotine molecules. When a person later uses tobacco, the anti-nicotine antibodies stop the nicotine molecules from entering the central nervous system and ever reaching the brain.

Though a vaccine wouldn't be a silver bullet—there would still be withdrawal symptoms—a person may be less motivated to relapse because the brain's reward system could no longer react to nicotine.

The problem with the previous nicotine vaccine, which only worked in 30 percent of patients, was that it did not single out the most common form of nicotine for attack. Nicotine has two forms that look like mirror images of each other—one is a "right-handed" version and one is a "left-handed" version. Even though 99 percent of the nicotine found in tobacco is the left-handed version, the previous vaccine elicited antibodies against both.

Janda believes that was a waste of immune response. "This is a case where something very simple was overlooked," he said.

Improving the Response

In the new study, the researchers elicited a more robust antibody response by creating a vaccine from only left-handed nicotine haptens. To do this, they prepared haptens as a 50-50 mixture and as pure right-handed or pure left-handed versions of nicotine, so they could use the two versions together or separately.

They tested both versions and the 50-50 mix in rat models, injecting the rats three times over 42 days. This series of "booster" shots gave the animals' immune systems a chance to create an effective number of antibodies to respond to nicotine.

The researchers analyzed blood from the three experimental groups and

found that the left-handed hapten elicited a much more effective immune response. Compared with the right-handed hapten vaccine, the left-handed hapten vaccine prompted the body to create four times as many antibodies against left-handed nicotine molecules. The 50-50 mix was only 60 percent as effective as the pure left-handed version.

"This shows that future vaccines should target that left-handed version," said Jonathan Lockner, research associate in the Janda lab and first author of the new paper. "There might even be more effective haptens out there."

The researchers believe purifying nicotine hapten mixtures is an important and practical step in creating future nicotine vaccines. Janda said considering molecule handed-ness is also critical for developing vaccines against other drugs of abuse, such as cocaine and heroin.

"This is just one area where we are looking outside the box to try to treat addiction," Janda said.

More information: "A Conjugate Vaccine Using Enantiopure Hapten Imparts Superior Nicotine-Binding Capacity,", pubs.acs.org/doi/abs/10.1021/jm501625j

Provided by The Scripps Research Institute

Citation: Scientists design nicotine vaccine that provokes robust immune response (2015, January 12) retrieved 5 May 2024 from https://medicalxpress.com/news/2015-01-scientists-nicotine-vaccine-provokes-robust.html

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