Medical Xpress

Scientists show that nicotine withdrawal reduces response to rewards across species

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Cigarette smoking is a leading cause of preventable death worldwide and is associated with approximately 440,000 deaths in the United States each year, according to the U.S. Centers for Disease Control and Prevention, but nearly 20 percent of the U.S. population continues to smoke cigarettes. While more than half of U.S. smokers try to quit every year, less than 10 percent are able to remain smoke-free, and relapse commonly occurs within 48 hours of smoking cessation. Learning about withdrawal and difficulty of quitting can lead to more effective treatments to help smokers quit.

In a first of its kind study on nicotine addiction, scientists measured a behavior that can be similarly quantified across species like humans and rats, the responses to rewards during nicotine withdrawal. Findings from this study were published online on Sept. 10, 2014 in *JAMA Psychiatry*.

Response to reward is the brain's ability to derive and recognize pleasure from natural things such as food, money and sex. The reduced ability to respond to rewards is a behavioral process associated with depression in humans. In prior studies of nicotine withdrawal, investigators used very different behavioral measurements across humans and rats, limiting our understanding of this important brain reward system.

Using a translational behavioral approach, Michele Pergadia, Ph.D., associate professor of clinical biomedical science in the Charles E. Schmidt College of Medicine at Florida Atlantic University, who completed the human study while at Washington University School of

Medicine, Andre Der-Avakian, Ph.D., who completed the rat study at the University of California San Diego (UCSD), and colleagues, including senior collaborators Athina Markou, Ph.D. at UCSD and Diego Pizzagalli, Ph.D. at Harvard Medical School, found that nicotine withdrawal similarly reduced reward responsiveness in human smokers - particularly those with a history of depression - as well as in nicotine-treated rats.

Pergadia, one of the lead authors, notes that replication of experimental results across species is a major step forward, because it allows for greater generalizability and a more reliable means for identifying behavioral and neurobiological mechanisms that explain the complicated behavior of nicotine withdrawal in humans addicted to tobacco.

"The fact that the effect was similar across species using this translational task not only provides us with a ready framework to proceed with additional research to better understand the mechanisms underlying withdrawal of nicotine, and potentially new treatment development, but it also makes us feel more confident that we are actually studying the same behavior in humans and rats as the studies move forward," said Pergadia.

Pergadia and colleagues plan to pursue future studies that will include a systematic study of depression vulnerability as it relates to reward sensitivity, the course of withdrawal-related reward deficits, including effects on relapse to smoking, and identification of processes in the brain that lead to these behaviors.

Pergadia emphasizes that the ultimate goal of this line of research is to improve treatments that manage nicotine withdrawal-related symptoms and thereby increase success during efforts to quit.

"Many smokers are struggling to quit, and there is a real need to develop

new strategies to aid them in this process. Therapies targeting this reward dysfunction during withdrawal may prove to be useful," said Pergadia.

More information: Pergadia, M.L., Der-Avakian, A., D'Souza, M., Madden, P.A.F., Heath A.C., Shiffman, S., Markou, A., Pizzagalli, D.A. (in press). Association between nicotine withdrawal and reward responsiveness in humans and rats. *JAMA Psychiatry*. DOI: 10.1001/jamapsychiatry.2014.1016. Published online September 10, 2014.

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