

## Scientists find blocking a neuropeptide receptor decreases nicotine addiction

November 24 2008

The study was published in an online Early Edition issue of the *Proceedings of the National Academy of Sciences*, the week of November 24. Scripps Florida is a division of The Scripps Research Institute.

The neuropeptide, hypocretin-1 (Orexin A), may initiate a key signaling cascade, a series of closely linked biochemical reactions, which maintains tobacco addiction in human smokers and could be a potential target for developing new smoking cessation treatments.

"Blocking hypocretin-1 receptors not only decreased the motivation to continue nicotine use in rats, it also abolished the stimulatory effects of nicotine on their brain reward circuitries," said Paul Kenny, Ph.D., the Scripps Research scientist at Scripps Florida who led the study. "This suggests that hypocretin-1 may play a major role in driving tobacco use in smokers to want more nicotine. If we can find a way to effectively block this receptor, it could mean a novel way to help break people's addiction to tobacco."

Cigarette smoking is one of the largest preventable causes of death and disease in developed countries, and accounts for approximately 440,000 deaths and \$160 billion in health-related costs annually in the United States alone. Despite years of health warnings concerning the well-known adverse consequences of tobacco smoking, only about ten percent of smokers who attempt to quit annually manage to remain smoke free after one year, highlighting the difficulty in quitting the smoking habit.



In the study, Kenny and a postdoctoral fellow in his laboratory, Jonathan Hollander, Ph.D., blocked the hypocretin-1 receptor using low doses of the selective antagonist SB-334867, a commercially available compound often used in research.

"While hypocretin 2 systems, otherwise known as orexin B, have been mainly implicated in regulating sleep," Kenny said, "hypocretin 1, also known as orexin A, appears to be more involved in regulating motivated behavior. Our previous studies in close collaboration with other Scripps Research scientists have shown that hypocretin-1 receptors play a central role in regulating relapse to cocaine seeking. With that in mind, it seemed reasonable to test whether it was involved in nicotine reward as well."

The new study indeed showed that blocking the receptor in rats significantly decreased nicotine self-administration and also the motivation to seek and obtain the drug. These findings suggest that hypocretin-1 receptors play a critical role maintaining nicotine-taking behavior in rats, and perhaps also in sustaining the tobacco habit in human smokers.

In addition, the study highlighted the importance of hypocretin-1 receptors in a brain region called the insula, a walnut size part of the frontal lobe of the brain. A highly conserved brain region, all mammals have insula regions that sense the body's internal physiological state and direct responses to maintain homeostasis. The insula has also been implicated in regulating feelings of craving. In a recent groundbreaking study, it was reported that smokers who sustained damage to the insula lost the desire to smoke, an insight that revealed the insula as a key brain region that sustains the tobacco habit in smokers. Until the new study, however, the neurobiological mechanisms through which the insula regulated the persistence of tobacco addiction remained unclear.



The new study sheds light on this question, showing that hypocretincontaining fibers project significantly to the insula, that hypocretin-1 receptors are expressed on the surface of neurons in the insula, and that blockade of hypocretin-1 receptors in the insula, but not in the adjacent somatosensory cortex region (which also records and relays sensory information), decreases nicotine self-administration. The effects of blocking hypecretin-1 receptors only in the insula, however, were less than blocking these receptors in the brain as a whole, suggesting that hypocretin transmission in other brain regions may also be playing a role in nicotine reward.

Working with scientists from Scripps Florida's Translational Research Institute, Kenny and his colleagues are now searching for new antagonists at hypocretin-1 receptors that are less toxic than the compound used in the published experiments in the hopes of furthering the development of a human therapy.

Source: Scripps Research Institute

Citation: Scientists find blocking a neuropeptide receptor decreases nicotine addiction (2008, November 24) retrieved 5 May 2024 from <u>https://medicalxpress.com/news/2008-11-scientists-blocking-neuropeptide-receptor-decreases.html</u>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.