Experimental drug found to reduce nicotine craving

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(Medical Xpress)—Researchers at the Aptuit Centre for Drug Discovery and Development in Italy, have found that a drug called GSK598809 is able to block a type of dopamine receptor in the brain that has been linked to nicotine addiction. The team, studying the impact of the drug on baboons and mice has found, as they describe in their paper published in the journal *Neuropsychopharmacology*, that when delivered to the brain, the drug appears able to reduce the cravings for nicotine found in the smoke of cigarettes and thus may someday soon serve as an aide to quitting the habit that kills millions the world over every year.

As with most addictions, the root cause of an addiction to nicotine is that it causes the release of dopamine into the brain which is picked up by

receptors. Over time the brain comes to expect the small dose to arrive in regular intervals and when it stops, severe cravings result that that make it extremely difficult to ignore. The result for many people is a long, lung destroying habit.

In this new research the team working out of a lab formerly owned by British drug-making giant, GlaxoSmithKline, tested the drug on baboons and rats by first getting them addicted to nicotine and then giving them GSK598809. They followed that up by performing brain scans which allowed them to see the actual impact of both the nicotine and drug on the brain. The results have been so promising that the team reports that they are now ready to begin clinical trials with people.

This new research was built on previous studies that showed that nicotine increased the release of dopamine into the pallidum, ventral striatum and midbrain, the parts of the brain that are now believed to be involved in nicotine addiction. GSK598809 doesn't prevent this from happening, but instead causes the brain receptors that react (D3 receptors) to not be so sensitive to its presence. Performing brain imaging allowed the researchers to see that the drug was making it to where it was supposed to go in the brain and to chart the amount of sensitivity that came about as a result; and because of this, the researchers were able to fine tune the amount of the drug needed to dull the addictive cravings in humans and actually ran a few test trials which they report did indeed reduce cravings in smokers.

The researchers say they believe GSK598809, once it undergoes more thorough testing, will one day be added to the list of drugs currently used to help people quit smoking and because it will prevent the associated cravings, will also help prevent relapse which is so common among those that try to quit.

More information: Occupancy of Brain Dopamine D3 Receptors and

Drug Craving: A Translational Approach, *Neuropsychopharmacology*, (12 September 2012) | doi:10.1038/npp.2012.171

Abstract

Selective dopamine D3 receptor (D3R) antagonists prevent reinstatement of drug-seeking behavior and decrease the rewarding effects of contextual cues associated with drug intake preclinically, suggesting that they may reduce drug craving in humans. GSK598809 is a selective D3R antagonist recently progressed in Phase I trials. The aim of this study was to establish a model, based on the determination of the occupancy of brain D3Rs (OD3R) across species, to predict the ability of GSK598809 to reduce nicotine-seeking behavior in humans, here assessed as cigarette craving in smokers. Using ex vivo [125I](R)-trans-7-hydroxy-2-[N-propyl-N-(3′-iodo-2′-propenyl)amino] tetralin ([125I]7OH-PIPAT) autoradiography and [11C]PHNO positron emission tomography, we demonstrated a dose-dependent occupancy of the D3Rs by GSK598809 in rat, baboon, and human brains. We also showed a direct relationship between OD3R and pharmacokinetic exposure, and potencies in line with the in vitro binding affinity. Likewise, GSK598809 dose dependently reduced the expression of nicotine-induced conditioned place preference (CPP) in rats, with an effect proportional to the exposure and OD3R at every time point, and 100% effect at OD3R values 72%. In humans, a single dose of GSK598809, giving submaximal levels (72–89%) of OD3R, transiently alleviated craving in smokers after overnight abstinence. These data suggest that either higher OD3R is required for a full effect in humans or that nicotine-seeking behavior in CPP rats only partially translates into craving for cigarettes in short-term abstinent smokers. In addition, they provide the first clinical evidence of potential efficacy of a selective D3R antagonist for the treatment of substance-use disorders.