Drug could stop marijuana cravings

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(Medical Xpress)—In the US, more people seek treatment for marijuana abuse than for abuse of cocaine or heroin. However, there are no approved treatments for marijuana addiction. Robert Schwarcz of the University of Maryland School of Medicine and his colleagues, including a group from the National Institute on Drug Abuse, have found a drug that appears to decrease the pleasurable effects of THC, marijuana's active ingredient, and could therefore prevent a psychological addiction to marijuana. The research appears in *Nature Neuroscience*.

THC produces a feeling of pleasure by increasing dopamine levels in the ventral tegmental area (VTA) and the shell of the nucleus accumbens (NAc). The researchers reasoned that if marijuana users took a drug that reduced dopamine activity in those regions of the brain, they would no longer experience a sense of euphoria when taking marijuana.

Therefore, their marijuana usage would decrease.

Schwarz and his team gave rats the drug Ro 61-8048, which increases the brain's level of kynurenic acid (KYNA), a byproduct of the breakdown of tryptophan, an amino acid found in turkey and other foods. The researchers found that Ro 61-8048 increased levels of KYNA in the VTA and NAc shell and reduced the ability of THC or WIN 55,212-2, a synthetic THC substitute, to stimulate dopamine production in these regions. KYNA appears to block dopamine receptors.

The team then taught rats to give themselves WIN 55,212-2 by pressing a lever. The rats pressed the lever frequently, a sign of addiction. When the researchers gave the rats Ro 61-8048, lever-pressing subsided. To test whether Ro 61-8048 could prevent a relapse, the researchers trained rats to self-administer WIN 55,212-2 and then stopped providing it after a while. Lever-pressing decreased significantly until the rats were given WIN 55,212-2 injections. Then, frequent lever-pressing resumed. However, when the team gave rats Ro 61-8048, this relapse behavior did not occur. The team achieved similar results with squirrel monkeys trained to press a lever to obtain THC.

Schwarcz and his colleagues concede that scientists must do further research before the FDA can approve Ro 61-8048 or similar drugs for use in humans. High levels of KYNA are associated with cognitive defects, so the treatment could be worse than the cure. Proponents of marijuana decriminalization would argue that frequent use of marijuana is not necessarily a problem requiring treatment. The large number of people seeking help for marijuana addiction could reflect the fact that the law requires people arrested for drug crimes to seek such help.

More information: Reducing cannabinoid abuse and preventing relapse by enhancing endogenous brain levels of kynurenic acid, *Nature Neuroscience* (2013) doi:10.1038/nn.3540

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Abstract

In the reward circuitry of the brain, α-7-nicotinic acetylcholine receptors (α7nAChRs) modulate effects of Δ9-tetrahydrocannabinol (THC), marijuana's main psychoactive ingredient. Kynurenic acid (KYNA) is an endogenous negative allosteric modulator of α7nAChRs. Here we report that the kynurenine 3-monooxygenase (KMO) inhibitor Ro 61-8048 increases brain KYNA levels and attenuates cannabinoid-induced increases in extracellular dopamine in reward-related brain areas. In the self-administration model of drug abuse, Ro 61-8048 reduced the rewarding effects of THC and the synthetic cannabinoid WIN 55,212-2 in squirrel monkeys and rats, respectively, and it also prevented relapse to drug-seeking induced by reexposure to cannabinoids or cannabinoid-associated cues. The effects of enhancing endogenous KYNA levels with Ro 61-8048 were prevented by positive allosteric modulators of α7nAChRs. Despite a clear need, there are no medications approved for treatment of marijuana dependence. Modulation of KYNA offers a pharmacological strategy for achieving abstinence from marijuana and preventing relapse.