Neural circuits underlying cannabis reward versus aversion

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Abstract: Objective Marijuana or cannabis has now been legalized in many states of the USA, although it remains unclear whether cannabis is safe or addictive. In humans, cannabis is not always rewarding. Instead, the drug makes some people feel unpleasant, depressed and anxious. Since abuse liability is one of the major concerns surrounding cannabis use, recent studies have focused on cannabis reward and the underlying neural mechanisms. Paradoxically, most of the findings in experimental animals indicate that cannabis is not rewarding, but aversive in many cases, which is opposite to what we might expect from a drug with abuse liability. The neurobiological mechanisms underlying such paradoxical effects are poorly understood. Methods To further address these issues, we first used multiple animal models of addiction, including intravenous drug self-administration, conditioned place preference, locomotor sensitization, and electrical brain-stimulation reward, to evaluate and compare the rewarding effects of delta9-tetrahydrocannabinol (Δ9-THC, the major psychoactive component in cannabis) and other addictive drugs such as cocaine, heroin or nicotine under the same experimental conditions. Results We found that Δ9-THC, unlike other addictive drugs, is not rewarding, but aversive in the above behavioral assays in rodents. We then used in vivo brain microdialysis to measure nucleus accumbens dopamine (DA) response to the drugs and optogenetics to observe optical stimulation of midbrain DA neuron-induced brain-stimulation behavior. We found that the addictive drugs such as cocaine or heroin produced a dose-dependent increase, while (Δ9-THC produced a dose-dependent reduction in either DA response to the drugs or DA-dependent optical brain-stimulation behavior. When using CB1-KO and CB2-KO mice as controls, we found that this reduction in DA was mediated by activation brain CB2 receptors (CB2Rs), not CB1Rs. Next, using RNAscope in situ hybridization, immunocytochemistry, and electrophysiology, we found that CB2Rs are expressed in midbrain DA neurons and selective activation of brain CB2Rs inhibited DA neuron activity and DA-dependent behaviors. These findings, for the first time, suggest that brain CB2Rs may under cannabis aversion. In addition to the CB2Rs, the CB1Rs are also highly expressed in the brain, particularly in both inhibitory GABAergic neurons and excitatory glutamatergic neurons. Using the similar optogenetic approaches, we found that activation of the CB1Rs in GABAergic neurons by Δ9-THC produced rewarding effects via a GABAergic disinhibition of DA neurons, while activation of CB1Rs in glutamatergic neurons produced aversive effects by decrease of glutamatergic inputs onto DA neurons. Conclusion cannabis action depends on the final net effect of multiple actions, including GABAergic CB1R-mediated reward, glutamatergic CB1R-mediated aversion, dopaminergic CB2R-mediated aversion. These cell type-specific CB1 and CB2 receptor mechanisms may well explain why cannabis could be rewarding or aversive, since the cellular distributions of CB1 and CB2 receptors may be different in different species, strains or individuals.

Key words: Cannabis, Δ9-THC, dopamine, reward, addiction, CB1 receptor, CB2 receptor