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Dissecting the Role of Midbrain GABA Neurons in Cannabinoid Reward and Aversion Using Conditional CB1 Receptor Knockout Mice

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Cannabinoids produce both rewarding and aversive effects, yet the neural mechanisms underlying these outcomes are not fully understood. Cannabinoid reward has been thought to be mediated by activation of CB1 receptor (CB1R) on GABAergic neurons in the ventral tegmental area (VTA), leading to dopaminergic (DA) neuron disinhibition. However, behavioral evidence is lacking. Our previous research identified CB1R on midbrain glutamate and a subset of DA neurons as mediators of cannabinoid-induced aversion. This study further investigates the role of GABAergic CB1R in cannabinoid reward using conditional CB1-knockout (CB1-KO) mice and optogenetics. RNAscope in situ hybridization confirmed CB1R (mRNA) expression in VTA GABA neurons. Systemic administration of Δ9-THC produced conditioned place aversion (CPA) in both Vgat-Cre mice and Vgat-CB1-KO mice, suggesting that GABA neuron CB1R is not critical for aversion. Similarly, photoactivation of VTA GABA neurons produced aversive effects in real-time place preference tests, which Δ9-THC did not affect, indicating limited involvement of VTA GABA neurons in cannabinoid aversion. Optical inhibition of GABA neurons induced reward as assessed by optical intracranial self-stimulation, which was attenuated by Δ9-THC in Vgat-Cre but not in Vgat-CB1-KO mice. This contradicted our hypothesis that Δ9-THC would enhance optical stimulation reward by reducing GABA release via GABAergic CB1R. Lastly, GABA neuron apoptosis in the VTA, induced by AAV-caspase 3 in Vgat-Cre mice, did not impact Δ9-THC-induced CPA, hypoactivity, or analgesia. Together, these findings suggest that VTA GABAergic neurons are not essential for cannabinoid-mediated reward and aversion.