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Revisiting the cannabinoid-opioid interaction hypothesis using conditional CB1 and μ opioid receptor knockout mice

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The roles of the CB1 receptor (CB1R) in cannabinoid effects and the μ opioid receptor (MOR) in opioid effects are well characterized. Growing evidence indicates that co-administration of cannabinoids and opioids produces an enhanced analgesic effect; one hypothesis is that a direct interaction between membrane CB1R and MOR may underlie this phenomenon. Although numerous studies support this hypothesis, many others do not. The current study aims to address this discrepancy using conditional CB1R- or MOR-knockout mice. Our hypothesis is that if CB1R and MOR directly interact, then 1) both receptors should be co-localized on the same neurons and 2) selective deletion of one receptor should alter pharmacological or behavioral responses to activation of the other. Using RNAscope in situ hybridization, we found that mouse CB1R and MOR mRNA displayed distinct regional distributions. CB1R-MOR co-localization was observed in ~50% of paraventricular nucleus of the thalamus (PVT) glutamate neurons, ~35% of substantia nigra pars reticulata (SNr) GABA neurons, ~25% of ventral tegmental area (VTA) GABA neurons, and <10% of nucleus accumbens (NAc) GABA neurons. Using conditional knockout mice, we found that MOR deletion from GABA or glutamate neurons failed to alter Δ^9-THC-induced tetrad (analgesia, hypothermia, catalepsy, and immobility) effects, and CB1R deletion from GABA neurons also failed to alter oxycodone-induced analgesia and hypothermia. Additionally, deletion of CB1R or MOR from GABA or glutamate neurons failed to alter conditioned place preference or aversion to oxycodone or Δ^9-THC, respectively. Together, our findings do not support the CB1R-MOR interaction hypothesis.