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Brain CB2 receptor: a new therapeutic target for treating opioid use disorders, major findings from a new CB2-KO-eGFP reporter mouse line

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Brain CB2 receptors (CB2R) are thought to be mainly expressed in microglia. However, there is limited evidence of CB2R expression in microglia, and growing evidence indicates neuronal CB2R expression in rodents. There are two CB2-reporter mouse lines (BAC-based-CB2R-GFPTg and CB2-eGFP-flox-5xFAD) in which the CB2-GFP signal is detected in some microglia. However, concerns regarding whether GFP expression truly reveals endogenous CB2R expression in these mouse lines complicate data interpretation.

Here, we report a new CB2-KO-eGFP reporter mouse line in which the eGFP gene sequence replaces the endogenous CB2R-coding region. In this new mouse line, we detected high-density CB2-eGFP signals in midbrain dopamine (DA) neurons and cortical and subcortical glutamate neurons, whereas weak CB2-eGFP signals were detected in microglia.

Given the critical role of DA neurons in drug addiction, we explored the role of CB2R in opioid addiction-like behaviors in rodents. We found that CB2-KO-eGFP mice showed higher basal levels of locomotion than wild-type littermates; however, oxycodone-induced hyperlocomotion was unaffected. Systemic administration of MRI-2594, a novel CB2R agonist, produced analgesia in wild-type mice but not in CB2-KO-eGFP mice, and reduced intracranial self-stimulation maintained by optical stimulation of midbrain DA neurons in DAT-Cre mice. Pretreatment with MRI-2594 inhibited intravenous heroin self-administration in rats and wild-type mice but not in CB2-KO-eGFP mice, enhanced oxycodone-induced analgesia in wild-type mice, and inhibited heroin-triggered reinstatement of drug-seeking in rats. These findings suggest that brain CB2Rs are expressed mainly in DA and glutamate neurons and that MRI-2594 deserves further research as a new pharmacotherapy for opioid use disorders.