Name: Emmanuel Onaivi Email: ONAIVIE@WPUNJ.EDU

Dopaminergic and Microglia Cnr2 Gene Knockout Reveals Biased Neuroinflammation Signaling

Emmanuel S Onaivi[1], Berhanu G Kibret[1, 2], Shilpa Buch[3], Venkat Sharma[1], Qing-Rong Liu[4]

[1]William Paterson University, Wayne, NJ,
[2]University of Maryland School of Pharmacy, Baltimore, MD,
[3]University of Nebraska Medical Center, Omaha Nebraska,
[4]NIA-NIH, Baltimore MD

There exists some controversy, ambiguity, and lingering debate about the functional neuronal expression of cannabinoid CB2 receptors (CB2Rs). However, CB2Rs are expressed at low basal levels in the CNS, and they are dynamic, inducible and can be upregulated in neuropsychiatric and neurological disorders. As neuroinflammation is emerging as a key component underlying the effects of CB2Rs, we used Cre-LoxP technology to generate Cnr2 conditional knockout (cKO) mice with deletion of CB2Rs from microglia (CX3Cr1-Cnr2) and dopamine (DA) neurons (DATCnr2) respectively. The hypothesis that CB2Rs expressed in DA neurons and microglia differentially regulate drug induced behavioral deficits in CB2R cKO versus wild type (WT) mice was examined. DAT-Cnr2 cKO mice displayed exaggerated hyperpsychomotor responses and were insensitive to the rewarding effects of alcohol but not to cocaine, whereas CX3C1-Cnr2 cKO mice failed to display hyperactivity but were sensitive to the rewarding properties of alcohol and psychostimulants and exhibited increased weight gain compared to the WT mice. Cnr2 gene knockout mice revealed that CB2Rs are involved in the classical cannabinoid tetrad tests that was previously known to be associated with CB1R agonism. Biased cell-type CB2R signaling pathways were observed in dopaminergic and microglia specific CB2R deletions. Neuroinflammation pathways of PI3K/AKT/mTOR, MAP/ERK and NF-κB were differentially affected by cell-type specific deletion of CB2Rs in cerebral cortices of cKO and WT mice. CB2Rs upregulated the expression of NLRP3 inflammasome pathway. The studies implicate CB2R modulatory effects on neuroinflammation and may be potential therapeutic target in drug addiction and CNS disorders associated with neuroinflammations.