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Cannabinoid type 2 receptor neuro-immune crosstalk following microglia and dopaminergic neuron specific deletion of CB2Rs.

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CB2 cannabinoid receptor (CB2R) is a component endocannabinoid system (ECS) that plays a role in neuroinflammation. We utilized a battery of *in-vivo* behavioral tests, and *in-vitro* assays of immunoblotting, gene expression profiling, immunohistochemistry to determine the neuro-immuno-modulatory effects of CB2Rs. CB2R conditional knockout (cKO) mice with deletion of CB2Rs from dopamine neurons, DAT-*Cnr2* and those with deletion from microglia Cx3cr1-*Cnr2* displayed differential phenotypes. DAT-*Cnr2* cKO mice displayed hyper-psychomotor responses and were insensitive to the rewarding effects of alcohol but not to cocaine, whereas Cx3cr1-*Cnr2* cKO mice failed to display hyperactivity but were sensitive to the rewarding effects of alcohol and psychostimulants and exhibited increased weight gain compared to the DAT-*Cnr2* and wild type (WT) controls. Neuroinflammation pathways of PI3K/AKT/mTOR, MAP/ERK and NF-kβ were differentially affected by the cell-type specific deletion of CB2R in cerebral cortices of the cKO and WT mice. CB2Rs in dopamine neurons and microglia upregulated the expression of NLRP3 inflammasone pathway including NLRP3, cleaved caspase 1, and mature form of interleukin Il1β in striatal region compared with the WT controls. There was increased expression of proinflammatory cytokines TNF-α, IL-6, lL-1α, and IL-1β in the frontal cortices of the cKO mice following subacute treatment with 8% alcohol compared to the vehicle treated mice. In summary, selective deletion of CB2Rs from either dopamine neurons or microglia differentially modifies behavioral effects with biased inflammation signaling pathways. Thus, CB2 cannabinoid receptor neuroimmune crosstalk could be exploited as therapeutic targets in CNS disorders associated with neuroinflammation.

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