Type-1 cannabinoid receptors regulate inflammatory neurodegeneration in multiple sclerosis

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Multiple sclerosis (MS) is a chronic inflammatory disease affecting the central nervous system, and presenting both demyelinating and neurodegenerative features. Cannabinoid CB1 receptors (CB1Rs) play a substantial role in the control of synaptic mechanisms at the basis of the neurodegenerative damage observed in the experimental autoimmune encephalomyelitis (EAE), a reliable model of MS. To address the role of CB_1Rs in the pathophysiology of MS, we first investigated the effect of IL-1β, a pro-inflammatory cytokine released in response to lymphocyte infiltration and microglial activation in the brain, on the CB1R-mediated control of synaptic transmission. Secondly, we explored the impact of CB1Rs modulation on the inflammatory neurodegeneration processes responsible for irreversible disability in MS patients. We have found that IL-1β abrogated the sensitivity of CB1Rs controlling both glutamate and GABA transmission, through different mechanisms. IL1β-$CB1R_{(GABA)}$ and IL1β-$CB1R_{(glu)}$ interactions are in fact both dependent upon the PKC/TRPV1 pathway, but are differentially regulated by the BDNF- and trkB-dependent composition of membrane lipid rafts. The described interplay between IL1β and $CB1Rs_{(glu)}$ may play a role in cell damage by favoring excitotoxic neurodegeneration during central inflammatory diseases.
In line with this, genetic ablation of CB_1Rs exacerbates the neurodegenerative damage of EAE. The gene encoding CB_1R in humans (CNR1) has a AAT trinucleotide short tandem repeat polymorphism $(AAT)_n$ downstream of its translation site, which might be postulated to influence receptor expression. Our results provide evidence that long $(AAT)_n$ repeats within the CNR1 gene reduce CB_1R expression, and exacerbate the impact of inflammation on neuronal integrity and function in the optic nerve and in the brain of MS patients. MS subjects homozygous for the long allele of CNR1, in fact, had reduced CB_1R expression, and more pronounced neuronal degeneration in response to inflammatory white matter damage both in the optic nerve and in the cortex, especially in areas with a major role in cognition. Consistent with these findings, we found that these patients had worse visual outcome after an optic neuritis episode, and more severe cognitive deficits and cortical plasticity impairment in response to white matter brain lesion accumulation. Our results demonstrate the biological relevance of the $(AAT)_n$ CNR1 repeats on the expression of CB_1Rs, and their critical involvement in the inflammatory neurodegenerative damage of MS.