Palmitoylethanolamide increases CB2 receptor expression via PPAR-α

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The endogenous fatty acid amide palmitoylethanolamide (PEA) has been shown to exert anti-inflammatory and analgesic effects mainly through inhibition of pro-inflammatory compound release from mast cells, macrophages, and microglia (Luongo et al., 2013). Although several mechanisms of action have been proposed, indirect activation of the cannabinoid (CB) system is thought to be responsible for the effects of PEA observed in several pain models. Using cultured rat microglia and human macrophages, we evaluated whether PEA affects CB receptor expression. We showed that PEA treatment increases CB2 mRNA and protein expression levels through peroxisome proliferator-activated receptor-α (PPAR-α) activation. The involvement of PPAR-α was demonstrated through i) pharmacological PPAR-α manipulation, ii) PPAR-α mRNA silencing, and iii) molecular docking. Incubation of microglia with PEA also induced morphological changes associated with an anti-inflammatory phenotype, compared to the phenotype of untreated microglia. Moreover, we observed that chronic treatment with PEA significantly increased CB2R expression in the spinal cord of healthy animals and prevented the behavioural dysfunctions induced by peripheral nerve injury. These results provide evidence for a new mechanism of action for PEA, indirect regulation of CB2R expression.

Luongo L, Guida F, Boccella S, Bellini G, Gatta L, Rossi F, de Novellis V, Maione S. 2013. Palmitoylethanolamide reduces formalin-induced neuropathic-like behaviour through spinal glial/microglial phenotypical changes in mice. CNS Neurol Disord Drug Targets 12(1):45-54.