Palmitoylethanolamide increases CB2 receptor expression via PPAR-Î± and induces a reactive phenotype in microglial cells

M.E. Giordano1, F. Guida1, L. Luongo1, R. Romano1, G. Bellini2, S. Alameen1, S. Boccella1, P. Axerio-Cilies3, A. Rizzo4, R. Imperatore5, V. de Novellis1, V. di Marzo5, S. Maione1

1Department of Experimental Medicine, Section of Pharmacology L. Donatelli, Second University of Naples, Naples, Italy.
2Department of Women, Child and General and Specialistic Surgery, Second University of Naples, Naples, Italy.
3Brain Research Center, University of British Columbia, Vancouver, Canada.
4Department of Experimental Medicine, Section of Microbiology and Clinical Microbiology, Second University of Naples, Naples, Italy.
5Endocannabinoid Research Group, Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, Pozzuoli, Italy.

Microglial cells are the resident immune cells responsible for maintaining homeostasis in the central nervous system (CNS). The activation of microglia cells forms part of an early defense mechanism following injury or disease and it is characterized by morphological rearrangements, proliferation, chemotaxis towards the site of damage, and release of mediators. Increasing evidence indicates that microglial activation is heterogeneous, including either cytotoxic or neuroprotective effects (Franco et Fernàndez-Suàrez, 2015). In addition to the inflammatory component, microglia are also considered to be the professional phagocytes in the CNS, responsible for removing dying or apoptotic cells, myelin debris, and bacteria. It is well known that microglia express components of the endocannabinoid system, including receptors, ligands, and degradative enzymes. In particular, the CB type 2 receptor (CB2R) is tightly regulated on microglial surfaces in several pathological states. Indeed, selective CB2R stimulation inhibits microglial reactivity and promotes a neuroprotective phenotype.
Palmitoylethanolamide (PEA) is an endocannabinoid-like compound, which belongs to a class of fatty acid ethanolamides, that 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). PEA is produced by neurons and glial cells in the CNS and is involved in the endogenous neuroprotective mechanisms that are activated following tissue damage or inflammation (Skaper et al., 2013; Mattace Raso et al., 2014). 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. In the present study, using cultured rat microglia and human macrophages, we aimed to determine if PEA affects cannabinoid signaling, by focusing on CB2R expression, because of its wide expression on immune cells. We showed that PEA treatment increases CB2 mRNA and protein expression levels through peroxisome proliferator-activated receptor-Î± (PPAR-Î±) activation. The involvement of PPAR-Î± was demonstrated through pharmacological PPAR-Î± manipulation, PPAR-Î± mRNA silencing, and computational approach. Through indirect immunofluorescence analysis we showed that incubation of microglia with PEA also induced morphological changes (compared to the phenotype of vehicle-treated microglia) associated with a reactive phenotype. The same phenotype was found also in PPAR-Î± agonist treated cells, confirming the involvement of this receptor in the mechanism of action of PEA. Linked to this reactive state, PEA treated microglia exhibited increased phagocytosis and migratory activity, which are both essential for exerting anti-inflammatory action. All together, these results suggest the indirect regulation of microglial CB2R expression as a new possible mechanism of action for PEA. Moreover, the reactive phenotype induced by PEA treatment suggests that this drug can be explored as a useful tool for preventing the symptoms associated with neuroinflammation in CNS disorders.

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