Effects of 2-Pentadecyl-2-oxazoline (PEA-OXA), the oxazoline of PEA, in an experimental model of carrageenan-induced hindpaw inflammation: involvement of PPAR-Î±?

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N-acylethanolamines (NAEs) comprise a family of bioactive lipid molecules present in animal and plant tissues, with *N*-palmitoylethanolamine (PEA) having received much attention owing to its anti-inflammatory, analgesic and neuroprotective activities.

2-Pentadecyl-2-oxazoline (PEA-OXA), the oxazoline of PEA, reportedly modulates activity of *N*-acylethanolamine-hydrolyzing acid amidase (NAAA), which catabolizes PEA. Because PEA is produced on demand and exerts pleiotropic effects on non-neuronal cells implicated in neuroinflammation, modulating the specific amidases for NAEs (NAAA, in particular) could be a way to preserve PEA role in maintaining cellular homeostasis through its rapid on-demand synthesis and equally rapid degradation. This study provides the first description of PEA-OXA in both green and roasted coffee beans and Moka infusions, and its synthesis. In the first step, in an established model of carrageenan (CAR)-induced rat paw inflammation, PEA-OXA was orally active in limiting histological damage and thermal hyperalgesia 6 h after CAR intraplantar injection in the right hindpaw and the accumulation of infiltrating inflammatory cells. PEA-OXA appeared to be more potent compared to ultramicronized PEA given orally at the same dose (10 mg/kg). PEA-OXA markedly reduced also the increase in hindpaw myeloperoxidase activity, an index of polymorphonuclear cell accumulation in inflammatory tissues, and cytokines release in paw tissues. Moreover, the treatment with PEA-OXA significantly prevented CAR-induced IκB-Î± degradation, nuclear translocation of NF-κB p65, the increase in iNOS, COX-2, ICAM-1, and the activation of mast cells. In the second step of expriments, in order to better investigate whether the mechanism of action of PEA-OXA is related to activation of PPAR-Î± receptors, we performed new experiments in PPAR-Î± KO mice. In conclusion, NAAA modulators like PEA-OXA may serve to maximize availability of NAEs (e.g. PEA) while providing for recycling of the NAE components for further resynthesis.