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Palmitoylethanolamide promotes anti-inflammatory phenotype of macrophages and attenuates plaque formation in ApoE-/- mice

Authors:
P Rinne¹, M Rami¹, L Ring¹, S Steffens¹, ¹Institute for Cardiovascular Prevention (IPEK) - Munich - Germany,

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Introduction: The endogenous fatty acid amide palmitoylethanolamide (PEA) is a lipid-derived mediator, which does not bind to the cannabinoid receptors CB1 or CB2, but exerts potent anti-inflammatory effects by ligating type-α peroxisome proliferator-activated receptors (PPAR-α). PEA has shown to possess therapeutic potential in inflammatory disease models, but the role of PEA and its promise as a therapeutic agent in atherosclerosis remain unexplored.

Purpose: We aimed to evaluate the therapeutic potential of chronic PEA treatment in atherosclerotic mice.

Methods: The anti-inflammatory efficacy and mechanism of PEA were first investigated in primary bone marrow-derived macrophages (BMDM) under stimulation with lipopolysaccharides (LPS). As an in vivo approach, 6-8 week-old female apolipoprotein E deficient (ApoE-/-) mice on a high fat diet were treated with either vehicle or PEA (3 mg/kg/day) for 4 weeks. Lesion size and macrophage content of plaques were determined in aortic root sections. Furthermore, leukocyte subpopulations and cytokine expression levels at the tissue level were studied by flow cytometry and quantitative PCR, respectively.

Results: In LPS-stimulated BMDMs, PEA reduced the expression pro-inflammatory cytokines in a dose-dependent manner and through the activation of PPAR-α. Without affecting body weight or plasma cholesterol level, chronic in vivo administration of PEA was effective in attenuating atherosclerotic lesion size in ApoE-/- mice. Absolute macrophage-positive area of the lesions was also reduced in PEA-treated mice, but when normalized to total plaque area, macrophage content was comparable between the treatment groups. PEA treatment downregulated the expression of M1-type macrophage markers while enhancing M2 marker expression particularly in the spleen. Unexpectedly, PEA-treated mice had increased levels of classical monocytes in the circulation and aorta, an effect that occurred through a yet unknown mechanism.

Conclusions: Our data show that PEA evokes potent anti-inflammatory effects in cultured primary macrophages, which translates into an atheroprotective effect in a model of early atherosclerosis. Future studies will be instrumental to clarify the underlying mechanisms and to evaluate whether this treatment strategy has efficacy also in pre-established and more advanced atherosclerosis.