Arterioscler Thromb Vasc Biol. 2018 Nov;38(11):2562-2575.
doi: 10.1161/ATVBAHA.118.311185.

Palmitoylethanolamide Promotes a Proresolving Macrophage Phenotype and Attenuates Atherosclerotic Plaque Formation

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PMID: 30354245 DOI: 10.1161/ATVBAHA.118.311185

Abstract

Objective- Palmitoylethanolamide is an endogenous fatty acid mediator that is synthetized from membrane phospholipids by N-acyl phosphatidylethanolamine phospholipase D. Its biological actions are primarily mediated by PPAR-α (peroxisome proliferator-activated receptors α) and the orphan receptor GPR55. Palmitoylethanolamide exerts potent anti-inflammatory actions but its physiological role and promise as a therapeutic agent in chronic arterial inflammation, such as atherosclerosis remain unexplored. Approach and Results- First, the polarization of mouse primary macrophages towards a proinflammatory phenotype was found to reduce N-acyl phosphatidylethanolamine phospholipase D expression and palmitoylethanolamide bioavailability. N-acyl phosphatidylethanolamine phospholipase D expression was progressively downregulated in the aorta of apolipoprotein E deficient (ApoE$^{-/-}$) mice during atherogenesis. N-acyl phosphatidylethanolamine phospholipase D mRNA levels were also downregulated in unstable human plaques and they positively associated with smooth muscle cell markers and negatively with macrophage markers.

Second, ApoE$^{-/-}$ mice were fed a high-fat diet for 4 or 16 weeks and treated with either vehicle or palmitoylethanolamide (3 mg/kg per day, 4 weeks) to study the effects of palmitoylethanolamide on early established and pre-established atherosclerosis. Palmitoylethanolamide treatment reduced plaque size in early atherosclerosis, whereas in pre-established atherosclerosis, palmitoylethanolamide promoted signs of plaque stability as evidenced by reduced macrophage accumulation and necrotic core size, increased collagen deposition and downregulation of M1-type macrophage markers. Mechanistically, we found that palmitoylethanolamide, by activating GPR55, increases the expression of the phagocytosis receptor MerTK (proto-oncogene tyrosine-protein kinase MER) and enhances macrophage efferocytosis, indicative of proresolving properties. Conclusions- The present study demonstrates that palmitoylethanolamide protects against atherosclerosis by promoting an anti-inflammatory and proresolving phenotype of lesional macrophages, representing a new therapeutic approach to resolve arterial inflammation.

Keywords: atherosclerosis; cholesterol; fatty acids; inflammation; macrophages.

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