Lipoxygenation of Docosahexaenoic Acid. Characterization of a Docosatriene Active on Platelets and Adipocytes.

Ping Chen, Jennifer Lefils, Evelyne Véricel, Nathalie Bernoud-Hubac, Michel Lagarde, Michel Guichardant. Université de Lyon, UMR 870 Inserm / Insa-Lyon, Villeurbanne, France.

Docosahexaenoic acid (DHA) is a long-chain polyunsaturated fatty acid (PUFA) of the omega-3 series, and the main PUFA of the brain and retina. With eicosapentaenoic acid (EPA), DHA is recognized for its potential benefit in the cardiovascular system. Whereas EPA may play this role through its interaction with the arachidonic acid (ARA) cascade, notably *via* cyclooxygenases, DHA is not a substrate of cyclooxygenases but can be converted by various lipoxygenases. Recent works from the groups of Bazan and Serhan in the US have shown that docosatriene product from DHA, named protectin or neuroprotectin D1 (10R,17SdiOH- docosa-4Z,7Z,11E,13E,15Z,19Z-hexaenoic acid) exerts potent anti-inflammatory and neural protection.

We report here the characterization of an isomer (10S,17S-diOH-docosa-4Z,7Z,11E,13Z,15E,19Z-hexaenoic acid), called PDX, as the main soybean lipoxygenase docosatriene product from DHA. This structure has been assessed by a combination of HPLC, mass spectrometry and NMR approaches. We show that PDX inhibited platelet aggregation at submicromolar concentrations. When compared to a variety of isomers, including conjugated trienes issued from the lipoxygenation of ARA, it appears that the inhibition required a conjugated triene motif with the E,Z,E geometry whereas that with the E,E,Z geometry was inactive. Further studies using the 3T3-L1 adipocyte cell line showed that PDX is a strong stimulator of cell secretion of adiponectin, a potent anti-atherogenic adipokine.

Altogether, these results show that PDX, a soybean lipoxygenase docosatriene product, could have a relevant biological activity to fight athero-thrombogenesis.