Contribution of neuroprostanes to the anti-inflammatory properties of the omega-3 fatty acid DHA

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The anti-inflammatory properties of DHA have been largely demonstrated *in vitro* and *in vivo* but research gaps remain regarding the contribution of the oxygenated metabolites. Neuroprostanes (NeuroPs) are specific oxygenated metabolites produced by free-radical mediated peroxidation of DHA which might contribute to its anti-atherosclerotic and anti-inflammatory properties[1].

To confirm this hypothesis and to decipher the molecular mechanisms of action, human peripheral blood mononuclear cells were isolated from healthy donors by Ficoll density gradient centrifugation. Monocytes were differentiated into resting macrophages (RM) for 6 days (37°C, 5% CO_2). RM were exposed to 2 different types of NeuroPs (i.e. 14-A_4-NeuroP and 4-F_{4t}-NeuroP, 10 µM) or ethanol (vehicle 0.15%) during 30 min. Then LPS (100 ng/mL) was added for 6 hours to induced inflammatory response.

Both types of NeuroPs (14-A_4-NeuroP and 4-F_{4t}-NeuroP) significantly decreased the mRNA levels of IL-6 (-49% and -26% respectively) and MCP-1 (-55% and -24 % respectively). Secretion of TNFα and MCP-1 was also reduced when RM were exposed to 14-A_4-NeuroP (-10%, ns and -34%, $p<0.05$) and 4-F_{4t}-NeuroP (-12%, $p<0.01$ and 25%, ns). Preliminary results regarding the expression and phosphorylation of IκBα suggest that 4-F_{4t}-NeuroP could exert its anti-inflammatory effects through the inhibition of IκBα phosphorylation. Finally, cotransfection of luciferase reporter vector with hPPARγ expression vector performed on Cos-7 cells suggests that NeuroPs probably act independently of PPARγ.

In conclusion, these results challenge the long standing paradigm suggesting that peroxidized metabolites of PUFAs might only be cytotoxic molecules and show that NeuroPs contribute to the anti-inflammatory effects of DHA.

1. Gladine et al., Lipid Profiling Following Intake of the Omega 3 Fatty Acid DHA Identifies the Peroxidized Metabolites F4-Neuroprostanes as the Best Predictors of Atherosclerosis Prevention, PlosOne, 2014