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## **Neuroprostanes, produced by free-radical mediated peroxidation of DHA, inhibit the inflammatory response of human macrophages.**

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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. Among them, we are focusing on prostaglandin-like molecules termed Neuroprostanes (NeuroPs) which are produced through free-radical-mediated peroxidation of DHA. We hypothesized that these specific molecules which are highly reactive and produced in abundance during oxidative stress and inflammation could contribute to the anti-inflammatory properties of DHA.

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<sub>2</sub>). RM were exposed to 2 different types of NeuroPs (i.e. 14-A<sub>4</sub>-NeuroP and 4-F<sub>4t</sub>-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<sub>4</sub>-NeuroP and 4-F<sub>4t</sub>-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<sub>4</sub>-NeuroP (-10%, ns and -34%, p<0.05) and 4-F<sub>4t</sub>-NeuroP (-12%, p<0.01 and 25%, ns). Preliminary results regarding the expression and phosphorylation of IκBα suggest that 4-F<sub>4t</sub>-NeuroP could exert its anti-inflammatory effects through the inhibition of IκBα phosphorylation. Finally, cotransfection of luciferase reporter vector with hPPAR<sub>γ</sub> expression vector performed on Cos-7 cells suggests that NeuroPs probably act independently of PPAR<sub>γ</sub>.

In conclusion, these results suggest that the anti-inflammatory properties of DHA could be mediated, at least in part, by NeuroPs which corroborates the importance of oxidative stress in cell signaling.