Omega-3 fatty acids differentially alter the expression of detoxification enzymes and nitric oxide bioavailability in endothelial cells during IL-6 exposure

S.C.R. Sherratt[1], P. Libby[2], D.L. Bhatt[2], H. Dawoud[3], T. Malinski[3], R.P. Mason[2]

[1]Elucida Research LLC, Biophysics Department, Beverly, MA, United States of America; [2]Brigham and Women'S Hospital, Harvard Medical School, Boston, United States of America; [3]Ohio University, Department of Chemistry and Biochemistry, Athens, OH, United States of America

Funding Acknowledgement: Type of funding sources: Private company. Main funding source(s): Amarin Pharma Inc., Elucida Research

Background: Atherosclerotic plaques can elaborate reactive oxygen species (ROS) that reduce nitric oxide (NO) bioavailability. Cellular detoxification enzymes including various peroxiredoxin (PRDX) and superoxide dismutase (SOD) isoforms can inactivate ROS. The omega-3 fatty acid (n3-FA) eicosapentaenoic acid (EPA) reduced cardiovascular (CV) events in high-risk patients (REDUCE-IT), a benefit not observed with mixed n3-FAs containing docosahexaenoic acid (DHA).

Purpose: The purpose of this study was to compare the effects of EPA and DHA on NO bioavailability and expression of detoxification enzymes in the vascular endothelium in vitro.

Methods: Human umbilical vein endothelial cells (HUVECs) were pretreated with EPA or DHA at equimolar levels (10 μM) for 2 h, then challenged with IL-6 at 12 ng/ml for 24 h. Proteomic analysis was performed using LC/MS to measure relative protein expression. Only significant ($p<0.05$) changes between treatment groups >1-fold were analyzed. Cells were stimulated with calcium ionophore to measure NO and peroxynitrite (ONOO-) release using a porphyrinic nanosensor.

Results: EPA, but not DHA, augmented PRDX-2 and SOD1 expression in HUVECs relative to IL-6 alone (1.2-fold and 1.6-fold, respectively, p=0.03). EPA also significantly lowered other isoforms unlike DHA. Either EPA or DHA increased thioredoxin expression by 1.5-fold (p=0.001) and 1.3-fold (p=0.02), respectively and decreased SOD2 expression by 1.5-fold (p=8.75E-11) and 1.6-fold (p=6.03E-9), respectively. IL-6 alone only increased expression of 6 detoxification enzymes by at least 1.2-fold, relative to vehicle. Unlike DHA, EPA also increased the NO to ONOO- release ratio by 36% ($p<0.05$) relative to IL-6 alone, without changes in NO synthase (eNOS) expression.

Conclusions: n3-FAs differentially influenced NO bioavailability and expression of ROS detoxification proteins, including peroxiredoxin and SOD isoforms. The net benefits of EPA on eNOS function and ROS detoxification may contribute to reduced atherothrombotic risk compared to DHA.