The mechanisms of n-3 EPA/DHA supplementation on postprandial inflammatory response. The *in vitro* and clinical study.

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Mechanisms of beneficial effect of n-3 PUFA on development of T2D remain unresolved. Postprandial lipemia is risk for cardiovascular disease especially in subjects with metabolic syndrome (MetS). Insulin resistance – induced hyperglycemia and excess of circulating free fatty acids (FFA) is the hall-mark of glucolipotoxicity and lipid droplet (LD) formation in cells not devoted to metabolic substrate storage. Mitochondrial substrate overload induces free radical formation, endoplasmic reticulum (ER)-stress, changes in mitochondrial membrane potential ($\Delta\psi$), and LD formation. The fluctuating changes in mitochondrial membrane potential (MMP) induces autophagy promoting lysosomal degradation of modified proteins and lipids - the important mechanisms for cell survival and protection from apoptosis and cellular death. Dietary FFAs (PA, OA, except EPA) induces formation of different to preadipocytes of SVF (TG- rich) type of LD than in endothelial cells (the phospholipids - rich) LD. The bioinformatics analysis of microarray (Agilent) and lipidomic (MS/MS) results revealed an different (in comparison with the other FA) ability of EPA to modify the ER-stress, apoptosis, angiogenesis - related gene clusters in SVF vs. endothelial cells. All used FFAs, activated autophagy - related genes (i.e. chaperones*, LAMP2*) expression. Additionally n-6 AA induced the lipodystrophy gene Lpin what may explain the decreased accumulation of LD in SVF in presence of this FA. Thus EPA protects endothelial cells against the FFA-induced lipotoxicity by accelerating glucose uptake and metabolism, protects against mitochondrial impairment, ER stress and in consequences against the stress-induced LD phospholipidosis, cellular dysfunction and death. The effect of changes in sphingomyelin, ceramide and phospholipids composition (length of incorporated FFA) is noticed.

The three month EPA/DHA (1.24 g/d) supplementation during the high saturated FA or isocaloric carbohydrate rich diets normalize postprandial plasma lipids, and attenuate the oxidative stress in fasting and/or postprandial state in patients with MetS. (*Hartwig, Dembinska-Kiec 2010. The LIPGENE Study*). The three months of intervention study with EPAX 1050TG (DHA:EPA ratio 5:1; 1.8 g/day) supplementation under low-calorie diet resulted with statistically significant reduction of BMI as well as TG levels. The increased postprandial incretin: GIP AUC ($p=0,05$) during oral lipid tolerance but not oral glucose tolerance test was observed (*The BIOCLAIMS Study*).

Conclusion: The polyvalent effects of n-3 EPA/DHA supplementation maybe result of the modification of the cellular ERstress induced by metabolic substrate overload (i.e. glucolipotoxicity in postprandial period), decrease of stress-induced LD formation and modification of cellular signaling due to the changes in physico-chemical properties of cellular membrane phospholipids forming rafts as well as exosomes/microparticles serving for intercellular communications (*Mueller 2010*).

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