Modulations of Aortic and Hepatic Transcriptomes by Docosahexaenoic Acid during Atherosclerosis Dvelopment: Are There Some Dose/response Effects?

C. Gladine, N. Roy , B. Sion, B. Laillet, JP. Rigaudière, B. Morio, B. Comte, JM. Chardigny, INRA, UMR 1019 Nutrition Humaine, France.

Since the early studies in Greenland Eskimos, many studies have confirmed the association between consumption of long chain omega 3 polyunsaturated fatty acids (LC-ω3PUFA: eicosahexaenoic acid (EPA) and docosahexaenoic acid (DHA)) and decreased risk of cardiovascular diseases (*He et al., 2004*). The anti-atherosclerotic effects of LC-ω3PUFA mainly contribute to their cardioprotective potential and several studies demonstrated that LC-ω3PUFA act (directly or indirectly) as modulators of pro-atherogenic genes (e.g. endothelial leukocyte adhesion molecules, inflammatory cytokines and cyclooxygenase-2) and other hepatic genes involved in lipid metabolism and oxidative stress (*De Caterina et al., 1995*). However, the dose/response effects of LC-ω3PUFA on atherosclerosis development and modulations of gene expression as well as their mechanism of action are not well understood. Indeed, LC-ω3PUFA are oxidized (enzymatically or not) in many different lipid mediators whose bioactivity on the overall gene expression has not yet been fully investigated. Moreover, the quantity and quality of lipid mediators produced from LC-ω3PUFA may differ according to the type and the amount of LC-ω3PUFA ingested but also the patho(physio)logical status.

In the present study, we aimed to investigate the effects of increasing intakes of DHA on atherosclerosis development and the associated modulations of the aortic and hepatic transcriptomes. Twenty four New Zealand White rabbits were fed a high cholesterol diet (5 g of cholesterol/kg diet) for 7 weeks and, depending on the group distribution, animals received for the same period and by daily gavages (2 mL): oleic sunflower oil (Control group, n=6); or a mixture of oleic sunflower oil and tuna oil providing 0.05% (DHA-A group), 0.1% (DHA-B group) or 1% (DHA-C group) of daily energy intake as DHA. Atherosclerosis development was determined by measuring the accumulation of cholesterol ester into the arterial wall and transcription profiling. Extracted aorta and liver RNA was hybridised to Agilent rabbit 44K oligonucleotide arrays using a loop design. Differentially expressed genes in the liver and aorta were identified using Bioconductor (Moderated $p<0.05$, Fold Change (FC)>1.20) and clustered into pathways (Ingenuity Pathway Analysis 7.0). Biological interpretation of data is in progress and will be presented at the EuroFed Lipid congres.

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