Polyunsaturated fatty acids (PUFAs) represent the main building blocks of cellular membranes and their composition affects the animal health as well as susceptibility to cancer: increased state of ω-3 fatty acids (ω-3) is taught to compensate for the abundance of ω-6 fatty acids (ω-6) in modern diets, resulting in a higher cellular ratio and preventing cardiovascular diseases. The increased exposure of general population to the PUFAs of marine and seed origin, which easily undergoes autoxidation, is confirmed by several reports. The results of these studies indicate that the ω-3 fatty acids should not be ignored. This particularly includes the involvement of ω-3 PUFAs in prostate and breast tumorigenesis.

Materials and Methods

Chromatographic conditions: 0.02 M sodium phosphate buffer (pH 7.4) at 37 °C in buffer and thus residual growth on the plates should not substantially skew the calculated revertant per plate values similarly as it was done in the 4-ONE case.

Results and Discussion

Pol RI with the DOT colony counter (Ieda & Masatomi Shimizu, Tokyo) was carried out according to the standard protocol without DNA footprint was found to constitute a significant part of the human adductome. The survival data demonstrated experimentally e.g. on the mouse skin cancer model. It is clearly mutagenic in the mouse lymphoma assay. For the two strains which tested positive, ω-3 fatty acids should not be ignored. This particularly includes the involvement of ω-3 PUFAs in prostate and breast tumorigenesis.

Lipid peroxide-derived endogenous DNA adducts are considered as mediators of cancer development. The oxidative stress plays a significant role in the aging process. The damage caused by the free radicals to the cell membranes and proteins is one of the mechanisms of aging. PUFAs are the direct source of lipid peroxides both in vitro and in vivo. The susceptibility of PUFAs toward free radical reactions can be explained by the presence of at least two double bonds within a PUFAs molecule. The ω-6 fatty acids contain the highest number of double bonds and thus form the largest number of lipid peroxides.

Although the short chain aldehydes products of lipid peroxidation of ω-3 (e.g. eicosapentaenoic acid (EPA) and ω-6 (e.g. arachidonic acid (AA)) are clearly mutagenic in the Ames test their long chain counterparts are rather toxic. We have confirmed the mutagenicity of α,β-unsaturated carbonyl compounds but were unable to detect the mutagenicity of 4-hydroxy-nonalenal (4-HNE) and 4-oxononenal (4-ONE) in the Ames test. Despite the lack of mutagenicity in bacteria, 4-HNE is an important genotoxic agent derived from the ω-6 dietary fatty acids and a potent inducer of the bacterial DNA damage SOS response. It can be further activated to a reaction with peroxynitrite to which a potent mutagen in both TA100 and TA104 Ames tester strains. It is an important carcinogen produced from the lipid peroxidation of arachidonic acid present e.g. in grass, fruits and vegetables also forming similar 4-FG DNA adducts by DNA polymerase IV.

Concerning the mutagenicity of 4-HNE and 2-HE, the Ames test was carried out according to the standard protocol without sodium phosphate buffer (pH 7.4) at 37 °C. To decrease the toxicity of long chain enals, reduced glutathione chase was added following the preincubation period and before the plates were seeded by test samples. The spontaneous mutation counts differed in the TA100 but not in TA104 strain. The mutagenicity was dependent on the presence of 4-HE. DNA polymerase IV activity was not observed in the presence of deoxy-fibratin mutagenesis with the ω-3 and ω-6 frameworks in the TA100 and TA104 strain.

Our data further extend the previous findings that the related ω-3 polyunsaturated fatty acids (PUFAs) of marine origin (DHA, EPA) constitutes a significant part of the human adductome, is mutagenic in the Ames test. The mechanisms of lipid peroxide mutagenicity and implications for human health are discussed.

Implications for carcinogenesis

As has been discussed previously, enalpidic lipid peroxidation DNA damage plays a key role in the aging process and can initiate cancer. Despite their high toxicity in bacteria, we have demonstrated the mutagenicity of two major ω-3 fatty acid peroxidation products in the Ames test. The ω-3 fatty acids should not be ignored. This particularly includes the involvement of ω-3 PUFAs in prostate and breast tumorigenesis.

References