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THIYL RADICAL-INDUCED *CIS-TRANS*-ISOMERIZATION OF ARACHIDONIC ACID INHIBITS PROSTAGLANDIN METABOLISM

S. Kratzsch, K. Drößler, H. Sprinz, O. Brede

University of Leipzig, Institute of Zoology and Interdisciplinary Group Time-Resolved Spectroscopy, Germany

Thiyl radicals radiolytically generated from thiophenol in methanolic solution are known to isomerise double bonds of poly-unsaturated fatty acids (PUFA). γ-irradiating of such a system containing all-*cis* 5,8,11,14 eicosatetraenoic acid (arachidonic acid, AA) with low doses (0.1-0.8 kGy) results in a mixture of 8 to 32 % mono-*trans*-isomers. Here we report about the influence of mono-*trans*-AA on the primary steps of AA-metabolism and prostaglandin synthesis, catalysed by cyclooxygenase (COX). In the cell-free model system the reaction of COX-1 with AA was analysed by controling the oxygen level during the enzymatic reaction. As an example, a mixture of a low quantity of mono-*trans*-isomerized AA (10 %) and 90 % all-*cis*-isomer exhibits a marked reduced oxygen consumption by 45 %. As further proofs - the yield of reactive oxygen species (ROS) generated by the COX-coupled peroxidase reaction was detected, - and the COX-1 activity in presence of different amounts of *trans*-AA was characterized using a photometric assay based on the oxidation of TMPD. All these methods indicated semiquantitatively a reduced activity of COX-1, depending on the *trans*-isomer yield. Therefore, an inhibition of COX-1 activity by only one *trans*-double-bond in AA could be concluded.

Furthermore, *in vitro* cell-line experiments were performed analysing the influence of mono-*trans*-isomerized AA on the activity of the cell-own COX-2. Hence, VD_3-differentiated and LPS-stimulated monocyte-like cells were incubated with mono-*trans*-AA and ROS-production was detected by the chemiluminescence measurements mentioned above. Compared to the reaction with *all*-cis-AA we found a considerable lowered formation of ROS. Likewise, we obtained a reduced PGE_2-expression between 15 and 40 % for cells treated with 8 to 29 % *trans*-AA. The model as well as *in vivo* experiments demonstrate an inhibition effect of mono-*trans*-AA and give rise for postulating an enzyme blocking mechanism for COX-1 and COX-2 by *trans*-isomers.