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HYDROXYTYROSOL, AN OLIVE OIL PHENOLIC COMPOUND, INHIBITS CYCLOOXYGENASE-2 TRANSCRIPTION IN PHORBOL-ESTER-TREATED HUMAN MONOCYTES

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Introduction: Inflammation plays a critical role in atherosclerotic plaque development and instability. Cyclooxygenase(COX)-2 is a key mediator of inflammation. It is up-regulated in activated monocytes and macrophages of human atherosclerotic lesions. The extra-virgin olive oil is a source of bioactive compounds which can be responsible of Mediterranean diet athero-protective effect. Aim of the study was to examine the effects of hydroxytyrosol (HT), a phenolic compound from olives and extra-virgin olive oil, on COX-2 expression in phorbol-ester stimulated monocytic-macrophagic cells and to explore the mechanisms involved.
Methods: U937 monocytoid cells were pre-treated with HT (0-10 micromol/L) for 60 min before stimulation with 20 nmol/L phorbol myristate acetate (PMA) in RPMI 1640 medium with 5%SFB for 20 h. Cell supernatants were then tested for the release of PGE2 by EIA kit and cell extracts were analysed for COX-2 expression by Western blot analysis. COX-2 mRNA was investigated by semi-quantitative RT-PCR and COX-2 promoter activity was assessed by transient transfection of full length and partially deleted or mutagenized COX-2 promoter constructs.
Results: Stimulation of U937 cells with 20 nmol/L PMA for 20 h caused a marked increase in the production of prostaglandin(PG) E2. This effect was inhibited by 1 micromol/L HT both in PMA-treated U937 (by about 25%) and even more in U937 derived-macrophages (> 40%). Pre-treatment of U937 cells with 0.1-10 micromol/L HT reduced PMA-induced COX-2 protein and mRNA in a concentration dependent manner with a 30% reduction already at 1 mmol/L ($p<0.01$). HT inhibitory effect was isoform specific given that the constitutive COX-1 expression was not affected. In transient transfection assay, HT reduced PMA-induced COX-2 promoter activity of full length construct. Transient transfections utilizing COX-2 promoter deletion constructs and COX-2 promoter constructs, in which specific enhancer elements were mutagenized, indicated that the effects of HT were, at least in part, mediated via NF-kB elements.
Conclusions: HT inhibited PGE2 release and COX-2 expression in phorbol-ester-stimulated monocytes and U937-derived macrophages. These data provide new insight into the anti-inflammatory properties of HT and may contribute to explain the cardiovascular protection by specific components of Mediterranean diets.