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Hydroxytyrosol suppresses MMP-9 activity and expression in human monocytes. A mechanism for plaque stabilization by a olive oil component of Mediterranean diets

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Purpose: Mediterranean diets, of which olive oil is an important component, are associated with low prevalence of cardiovascula diseases. The production of inflammatory mediators, such as prostaglandin (PG) E2, the overexpression of the inducibl cyclooxygenase (COX)- 2 isoform and the activation of matrix metalloproteinase(MMP)-9 by macrophages likely contributes t plaque instability leading to acute coronary events. We studied the effects of the olive oil phenolic antioxidant hydroxytyrosol (HT on MMP-9 and COX-2 activity and expression in human monocytes and explored underlying mechanisms. Methods: Huma monocytes were treated either with 1-50 µmol/L HT for 60 min or with selective inhibitors of PKC or COX isoenzymes for 30 mi before stimulation with 30 nmol/L phorbol myristate acetate (PMA) for 24 h. Cell supernatants were tested for the release of MMP-9 PGE2 and TIMP-1 and -2 by ELISA and MMP-9 activity by zymography. Cell protein extracts were analyzed by Western analysi for COX-2 expression and for membrane translocation of PKCs and the NADPH oxidase p47phox subunit. We analyzed the activit of COX-2 promoter by transient transfection experiments and the.activation of the transcription factor Nuclear Factor(NF)-kappal by EMSA. Results: PMA and, to a lesser extent, PGE2, induced the release of MMP-9 in monocytes. Cell exposure to HT befor PMA stimulation reduced MMP-9 activity and expression (IC50 for HT of 10 micromol/L $p < 0.01$) without affecting the release c TIMP-1 and -2. Correspondingly, HT inhibited PMA-induced PGE2 production (by 54 ± 7%) and COX-2 expression (by 43 ± 5% without affecting COX-1. Inhibition by HT was mediated by the suppression of NF-kappaB and the NADPH oxidase p47phox an PKCα/β1 activation. Conclusions: Our findings show that HT, at concentrations nutritionally achievable, inhibits the expressio and the release of MMP-9 at least in part by the suppression of COX-2 dependent PGE2 pathway. Such effect occurs through th attenuation of PKCα/β1 and NADPH oxidase activation. Overall, such results contribute to explaining the vascular protective effec exerted by olive oil in Mediterranean diets.