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THE OLIVE OIL ANTIOXIDANT HYDROXYTYROSOL(HT) REDUCES THE MATRIX METALLOPROTEINASE-9 ACTIVITY AND EXPRESSION IN HUMAN MONOCYTOID CELLS THROUGHOUT A PROSTAGLANDIN(PG) E₂-DEPENDENT MECHANISMS

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Objectives: Olive oil HT is believed to be among the most active cardio-protective components of Mediterranean diets. Since the PGE₂-dependent secretion of metalloproteinase(MMP)-9 by macrophages plays a key role in matrix degradation underlying plaque instability, we studied the effects of HT on the release and activity of MMP-9 in cultured human monocytoid cells as a possible explanation to the olive oil vascular protective effect.

Methods: Human monocytoid cells were treated with 1-50 μmol/L HT or, alternatively, with selective inhibitors of PKC isoenzymes and cyclooxygenase(COX)-2 for 60 min before stimulation with phorbol myristate acetate (PMA) or PGE₂ for 24 h. Cell supernatants were then tested for the release of MMP-9, PGE₂ and tissue inhibitor of metalloproteinases (TIMP)-1 and -2, while cell extracts were analysed by Western blot for COX-2 expression and PKCs membrane translocation (as an index of PKCs activation).

Results: PMA and, to a lesser extent, PGE₂, induced the cell release of MMP-9. Cell exposure to HT (as well as to NS-398 and GÖ6976, inhibitors of COX-2 and PKCα and β respectively) before PMA stimulation reduced MMP-9 release (IC₅₀ for HT of 10 μmol/L p<0.01) without affecting the release of TIMP-1 and -2. Correspondingly, HT inhibited PMA-induced PGE₂ production (by 54±7%) and the expression of COX-2 (by 43±5%) without affecting COX-1. Furthermore, HT also reduced the membrane translocation of PKCα, which is critically involved in the expression of COX-2.

Conclusions: Our findings support the involvement of COX-2 derived PGE₂ in the expression of MMP-9 by monocyte-like cells and demonstrate that HT inhibits the expression and the release of MMP-9. This effect appears to be mediated by the interference by HT with the stimulated expression of COX-2 and, upstream of this, with the activation of PKCα. Overall, such results contribute to explaining the vascular protective effects exerted by olive oil in Mediterranean diets.