

P4929 : Hydroxytyrosol suppresses phorbol ester-induced matrix metalloproteinase-9 expression by inhibiting both PKC α / β 1 and NF- κ B activation in human monocytoid cells

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Objectives: Mediterranean diets, of which olive oil is an important component, are associated with low prevalence of cardiovascular diseases, but active dietary components and their mechanisms of action are incompletely understood. The local production of active matrix metalloproteinase (MMP)-9 by macrophages likely contributes to plaque matrix degradation and plaque instability, leading to acute coronary events. We sought to examine the effect of the olive oil phenolic antioxidant hydroxytyrosol (HT) on MMP-9 expression and activity in monocytoid cells and to explore mechanisms of action involved.

Methods: U937 human monocytoid cells were pre-treated with HT (0-100 μ mol/L) for 30 min before stimulation with 50 nmol/L phorbol myristate acetate (PMA) in a serum-free medium for 24 h or alternatively with inhibitors of PKC iso-enzymes or of the NF- κ B pathway. Cell supernatants were then tested for gelatinase activity by zymography. MMP-9 protein and mRNA expression was assayed by ELISA and RT-PCR. We assessed the activation of transcription factor Nuclear Factor (NF)- κ B by EMSA and Western analysis of nuclear extracts, and the activation of PKC iso-enzymes by membrane translocation analysis.

Results: HT (1-100 μ mol/L) reduced PMA-induced MMP-9 activity at zymography analysis in a concentration-dependent manner, with inhibitory concentration producing 50% of the effect (IC₅₀) at 10 μ mol/L ($p < 0.01$). In addition, 10 μ mol/L HT reduced MMP-9 protein release and mRNA levels by about (by $60 \pm 5\%$ and $40 \pm 7\%$, respectively, $p < 0.01$), without significantly affecting TIMP-1 and -2 release. HT (10 μ mol/L) also significantly inhibited NF- κ B activation (by $57 \pm 8\%$) and PMA-induced membrane translocation of PKC α and β 1 (by $50 \pm 8\%$ and $35 \pm 5\%$, respectively, for all, $p < 0.05$), suggesting a plausible mechanism for the downregulation of MMP-9 expression by HT.

Conclusions: HT, the major olive and olive oil phenolic antioxidant, inhibits MMP-9 expression and release, interfering with PKC α / β 1 and NF- κ B activation in human monocytoid cells. This may contribute to plaque stabilization, explaining at least in part the cardiovascular protection by specific components of Mediterranean diets.