

A synthetic hydroxypropenone inhibits nitric oxide, prostaglandin E2, and proinflammatory cytokine synthesis

ABSTRACT

HMP [3-(2-hydroxyphenyl)-1-(5-methyl-furan-2-yl) propenone] was evaluated for its ability to inhibit the synthesis of major proinflammatory mediators and cytokines in interferon-gamma (IFN-gamma)- and lipopolysaccharide (LPS)-induced RAW 264.7 cells and phorbol myristate acetate (PMA)-differentiated/LPS-induced U937 cells. HMP suppressed the production of nitric oxide (NO) with significant inhibitory effects at doses as low as 0.78 microM ($P < 0.05$). Prostaglandin E2 (PGE2) secretion was also inhibited at doses of 12.5 microM and above ($P < 0.01$). The secretion of both TNF-alpha and IL-6 were only inhibited at the highest dose used (25 microM; $P < 0.001$). IL-1beta secretion was also inhibited from 12.5 microM onwards ($P < 0.01$). This inhibition was demonstrated to be caused by down-regulation of inducible enzymes, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2), without direct effect upon iNOS or COX-2 enzyme activity. HMP only inhibited iNOS ($P < 0.001$) and IL-1beta ($P < 0.05$) gene expression at the highest tested concentration. HMP did not affect the secretion of chemokines IL-8 and monocyte chemoattractant protein-1 (MCP-1) and the anti-inflammatory cytokine IL-10. The most striking effect of HMP was its NO inhibitory activity and therefore we conclude that HMP is a selective inhibitor of iNOS.

Keyword: COX-2; Cytokines; Hydroxypropenone; INOS; RAW 264.7; U937